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Contents on Inside Cover

American Heart Journal

CONTENTS FOR JANUARY, 1947

Original Communications

Clinical Reports

Abstracts and Reviews

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American Heart Journal

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Original Communications

ELECTROCARDIOGRAPHIC STUDIES IN RHEUMATIC HEART DISEASE WITH REFERENCE TO INTERPRETATION OF MULTIPLE UNIPOLAR PRECORDIAL LEADS

SAFETY R. FIRST, M.D., ARTHUR W. STICKLE, M.D., AND ROBERT H. BAYLEY, M.D.
OKLAHOMA CITY, OKLA.

THE routine use of multiple unipolar precordial leads revealed the frequent occurrence of left ventricular hypertrophy, heart in the vertical position, and a clockwise rotation of the manifest mean electrical axis[1] (right axis deviation) in curves recorded from children with rheumatic heart disease. The idea that mitral stenosis is the leading factor in the production of right axis deviation, an electrocardiographic finding which is currently interpreted as evidence of right ventricular hypertrophy, is uniformly emphasized in texts on electrocardiography.[2-5]

METHOD AND MATERIAL

A comparison of relevant physical findings with teleroentgenograms and electrocardiograms was made. Study of the latter included a calculation of the mean electrical axis (A_{QRS}) and the electrical position of the heart and interpretation of multiple precordial leads V_1, V_2, V_3, V_4, V_5, and V_6. The precordial leads were recorded by utilizing the left arm terminal of the galvanometer for the exploring electrode and the right arm terminal for the reference electrode which was connected to a central terminal[6] formed at the union of three wires, each connected to an extremity (the arms and the left leg).[7] The positions explored were those specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.[8]

In a comprehensive study[9] of multiple precordial leads, it was found convenient to refer to the right or left side of the electrical precordium, according

From the Department of Medicine, School of Medicine of the University of Oklahoma.
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to whether the potential variations of the region specified are transmitted from the surface of the right or the surface of the left ventricle. When a lead yields potential variations which resemble those found both farther to the right and farther to the left, it is said to be of transition form, or to be recorded from the transition zone. The latter zone divides the right and left side of the electrical precordium and varies from position one through position six, according to the heart's position and to other factors. In this study we have followed this terminology in reference to "transition" and to the "right side" and "left side" of the "precordium."

Fifty patients with rheumatic fever were selected according to the following criteria:

1. A typical history of at least one attack of acute rheumatic fever.
2. Cardiac enlargement as evidenced by at least one of the following: physical signs, teleroentgenogram, or electrocardiographic examination.

RESULTS

Of the fifty selected patients, twenty-seven gave a history of repeated attacks of acute rheumatic fever for a period of several years. Twenty-three patients were examined during their initial attack, or shortly thereafter. The ages of the patients studied ranged from 4 to 29 years, with an average of 10 years. There were twenty-two male and twenty-eight female subjects. Cardiac enlargement was evidenced by physical signs in thirty-two, by teleroentgenogram in twenty-six, and by the electrocardiogram in forty-nine subjects. Of the latter group, right ventricular hypertrophy was evidenced in twenty-five and left ventricular hypertrophy in forty-one subjects. Both right and left ventricular hypertrophy occurred in nineteen subjects (Table I).

The electrical positions of the heart, classified according to Wilson and associates[9] are itemized as follows:

POSITION	NUMBER OF CASES
Vertical	19
Semivertical	17
Intermediate	8
Semihorizontal	4
Horizontal	2
Indetermediate	0

The manifest mean electrical axis (A_{QRS}) showed clockwise rotation in twenty-one subjects, counterclockwise rotation in four, and normal axis in twenty-five. Eleven of the nineteen hearts which were classified as being in the vertical position yielded curves which showed evidence of right axis deviation in the limb leads and left ventricular hypertrophy in the precordial leads. The electrocardiograms of eight subjects indicated hypertrophy of both ventricles, heart in the vertical position, and clockwise rotation of A_{QRS}.

TABLE I. COMPARISON OF ELECTRICAL POSITION OF HEART, MANIFEST MEAN ELECTRICAL AXIS (A_{QRS}), AND SIZE OF HEART AS EVIDENCED BY ELECTROCARDIOGRAM, PHYSICAL SIGNS, AND TELEROENTGENOGRAM

ELECTRO-CARDIOGRAM	A_{QRS}	POSITION	PHYSICAL	TELEROENTGENOGRAM
L.V.P.	Right	Vertical	Marked enlargement	Slightly enlarged
L.V.P.	Right	Vertical	Normal	Normal
L.V.P.	Right	Vertical	Slight enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Slight enlargement	– – –
L.V.P.	Right	Vertical	Moderate enlargement	Normal
L.V.P.	Right	Vertical	Marked enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Marked enlargement	Markedly enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Slightly enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Normal
L.V.P.	Right	Vertical	Marked enlargement	Markedly enlarged
L.V.P.	Right	Semivertical	Normal	– – –
L.V.P.	Right	Semivertical	Marked enlargement	Moderately enlarged
L.V.P.	Left	Horizontal	Marked enlargement	Moderately enlarged
L.V.P.	Left	Semihorizontal	Marked enlargement	Moderately enlarged
L.V.P.	Normal	Semivertical	Moderate enlargement	Normal
L.V.P.	Normal	Semivertical	Marked enlargement	Markedly enlarged
L.V.P.	Normal	Semivertical	Moderate enlargement	Normal
L.V.P.	Normal	Intermediate	Moderate enlargement	Moderately enlarged
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Semihorizontal	Moderate enlargement	Moderately enlarged
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
Both	Right	Vertical	Normal	Slightly enlarged
Both	Right	Vertical	Slight enlargement	Normal
Both	Right	Vertical	Marked enlargement	Markedly enlarged
Both	Right	Vertical	Normal	Slightly enlarged
Both	Right	Vertical	Slight enlargement	Moderately enlarged
Both	Right	Vertical	Moderate enlargement	Moderately enlarged
Both	Right	Vertical	Slight enlargement	Slightly enlarged
Both	Right	Vertical	Normal	Normal
Both	Left	Semihorizontal	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Markedly enlarged
Both	Normal	Semivertical	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Moderately enlarged
Both	Normal	Semivertical	Normal	– – –
Both	Normal	Semivertical	Normal	Normal
Both	Normal	Semivertical	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Normal	Normal
Both	Normal	Intermediate	Normal	Normal
Both	Normal	Semihorizontal	Moderate enlargement	Normal
Normal	Normal	Semivertical	Marked enlargement	Moderately enlarged
R.B.B.B. (R.V.P.?)	Left	Horizontal	Moderate enlargement	Moderately enlarged

L.V.P., Left ventricular hypertrophy; R.V.P., right ventricular hypertrophy; Both, L.V.P. and R.V.P.; R.B.B.B., right bundle branch block; – – –, not taken.

Of the curves indicating the semivertical position, there were two with clockwise rotation of A_{QRS} and evidence of left ventricular hypertrophy in the precordial leads. Fourteen curves showed normal A_{QRS}. Of these, eight showed evidence of hypertrophy of both ventricles, two showed left ventricular hypertrophy, three showed right ventricular hypertrophy, and one was a normal electrocardiogram.

Of the four curves which displayed counterclockwise rotation of A_{QRS}, two occurred in hearts having the semihorizontal position, of which one presented additional evidence of left ventricular hypertrophy, and the other, hypertrophy of both ventricles. Of the remaining two curves which displayed counterclockwise rotation of A_{QRS} and horizontal positions, one showed left ventricular hypertrophy, whereas the other showed incomplete right bundle branch block.

ELECTROCARDIOGRAMS ILLUSTRATING VENTRICULAR HYPERTROPHY IN THE VARIOUS ELECTRICAL POSITIONS

Fig. 1 shows the electrocardiogram recorded during an attack of rheumatic fever from a 15-year-old white boy four years after the initial attack. Mitral systolic and diastolic murmurs, along with evidence of moderate cardiac enlargement, were detected on physical examination, although the roentgenograms showed a normal cardiac silhouette. The electrocardiogram shows a prominent R at V_5 and V_6 which indicates left ventricular hypertrophy. The electrical position of the heart is vertical, and clockwise rotation of A_{QRS} is present.

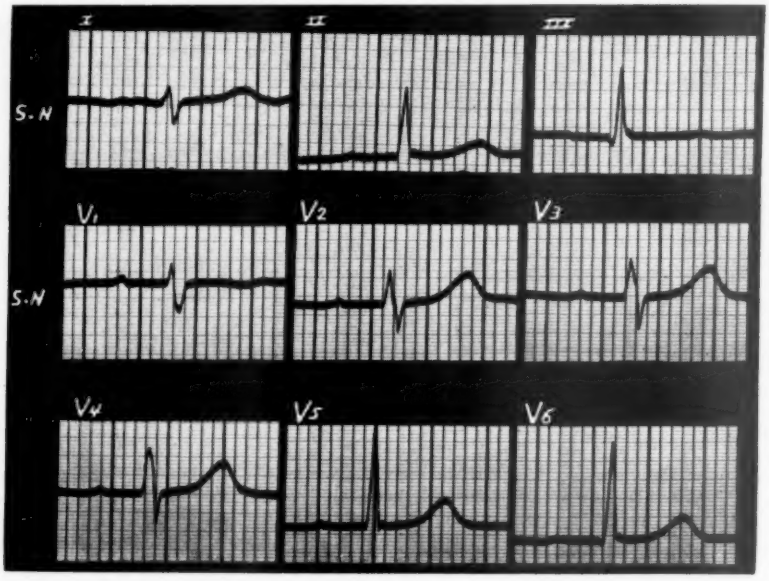

Fig. 1.—Child 15 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of A_{QRS}. V_1 and V_2 are from the right side of the precordium. Transition occurs at V_3. V_4, V_5, and V_6 are from the left side of the precordium.

It should be noted that the limb leads might have been interpreted as right axis deviation resulting from right ventricular hypertrophy, and the popular method of taking only one precordial lead, V_4, gives no added information inasmuch as the diagnostic deflection R is present only in V_5 and V_6.

Fig. 2 is the electrocardiogram recorded from an 11-year-old white girl three months following the onset of an initial attack of acute rheumatic fever. Soft, blowing systolic and diastolic mitral murmurs were detected along with physical and roentgenographic evidence of moderate cardiac enlargement. In the electrocardiogram, R and S are prominent in Leads V_2, V_3, and V_4 from the right side of the precordium, and R is also prominent at V_5 and V_6 from the left side of the precordium, indicating both right and left ventricular hypertrophy. The electrical position of the heart is semivertical, and A_{QRS} is normal. There is also prolongation of the P-R interval with primary T-wave changes which may be taken as additional evidence of active rheumatic myocarditis.

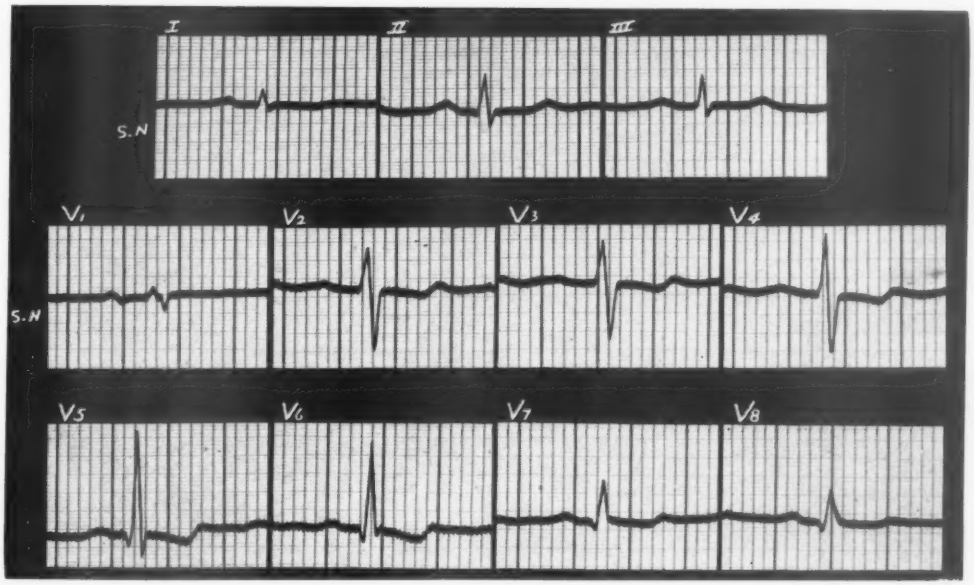

Fig. 2.—Child 11 years of age. Left and probably right ventricular hypertrophy; heart in the semivertical position; normal A_{QRS}. V_1, V_2, V_3, and V_4 are from the right side of the precordium. Transition occurs between V_4 and V_5. V_5, V_6, V_7, and V_8 are from the left side of the precordium.

Fig. 3 is the electrocardiogram recorded from a 9-year-old white girl during an acute attack of rheumatic fever, three years following the initial attack. On physical examination, harsh mitral diastolic and soft, blowing mitral and aortic systolic murmurs were detected. The blood pressure was 125/62, and there was both physical and roentgenographic evidence of moderate cardiac enlargement. The electrocardiogram shows a prominent S at V_1, V_2, and V_3. A prominent R occurs at V_5 and V_6 which are recorded at one-half normal stand-

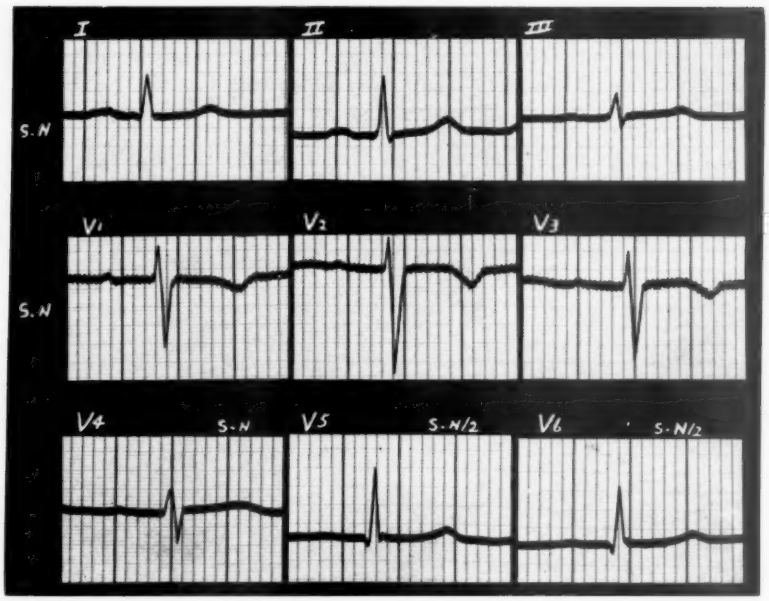

Fig. 3.—Child 9 years of age. Left ventricular hypertrophy; heart in the intermediate position; normal A_{QRS}. V_1, V_2, and V_3 are from the right side of the precordium. Transition occurs at V_4. V_5 and V_6, which are recorded at one-half normal standardization, are from the left side of the precordium.

ardization. These changes indicate left ventricular hypertrophy. The electrical position of the heart is intermediate, with normal A_{QRS}.

Fig. 4 is the electrocardiogram recorded from a 14-year-old white girl, who gave a history of repeated attacks of rheumatic fever accompanied by five years of cardiac decompensation. Physical examination revealed slight cardiac enlargement with a harsh presystolic mitral murmur extending through the first heart sound and accompanied by a palpable thrill. Teleroentgenograms were not made. The electrocardiogram shows a prominent S at V_2 and V_3 from the right side of the precordium, with a prominent R at V_5 and V_6 from the left side of the precordium, which indicate left ventricular hypertrophy. The electrical position of the heart is horizontal and counterclockwise rotation of A_{QRS} is present.

It is interesting to note that, in spite of mitral stenosis and congestive failure, left, rather than right, ventricular hypertrophy is present. Only one other patient in this series displayed a similar electrical position of the heart (Fig. 7).

ELECTROCARDIOGRAMS SUGGESTING TRANSIENT VENTRICULAR HYPERTROPHY

Figs. 5 and 6 show the electrocardiograms recorded from a 16-year-old white boy during the course of an initial attack of rheumatic fever. No murmurs were detected, and the heart did not appear to be enlarged on physical or roentgenographic examination. Fig. 5 shows a prominent S at V_2 and V_3, which indicates left ventricular hypertrophy. The electrical position of the heart is vertical,

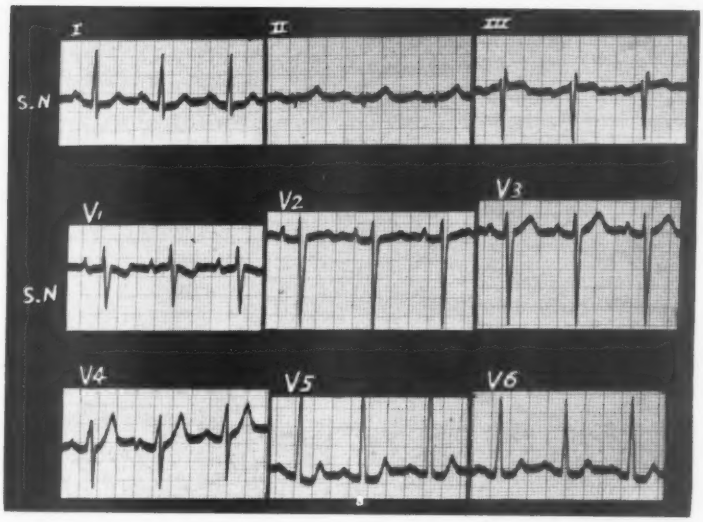

Fig. 4.—Child 14 years of age. Left ventricular hypertrophy; heart in the horizontal position; counterclockwise rotation of A_{QRS}. V_1, V_2, and V_3 are from the right side of the precordium. Transition occurs at V_4. V_5 and V_6 are from the left side of the precordium.

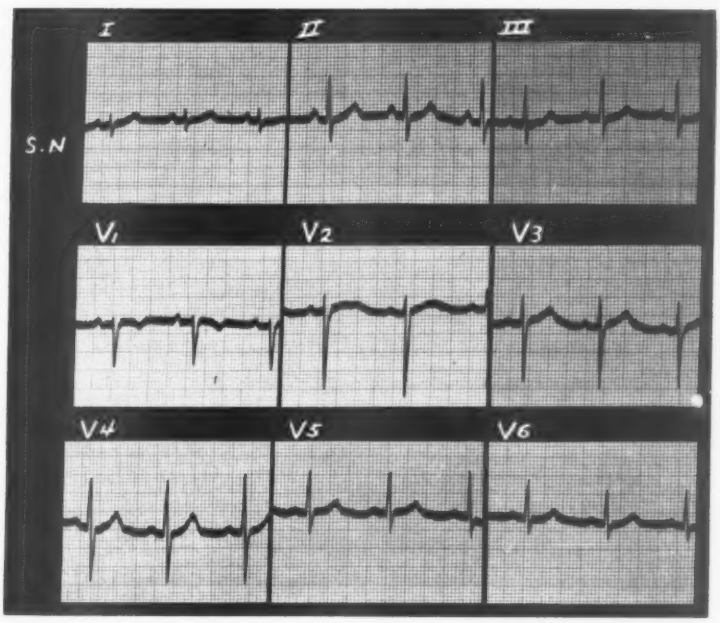

Fig. 5.—Adolescent boy 16 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of A_{QRS}. V_1, V_2, and V_3 are from the right side of the precordium. Transition occurs at V_4. V_5 and V_6 are from the left side of the precordium.

and there is a clockwise rotation of A_{QRS}. Fig. 6, recorded thirty days later, shows a normal electrocardiogram, in which the electrical position is semivertical and A_{QRS} is normal.

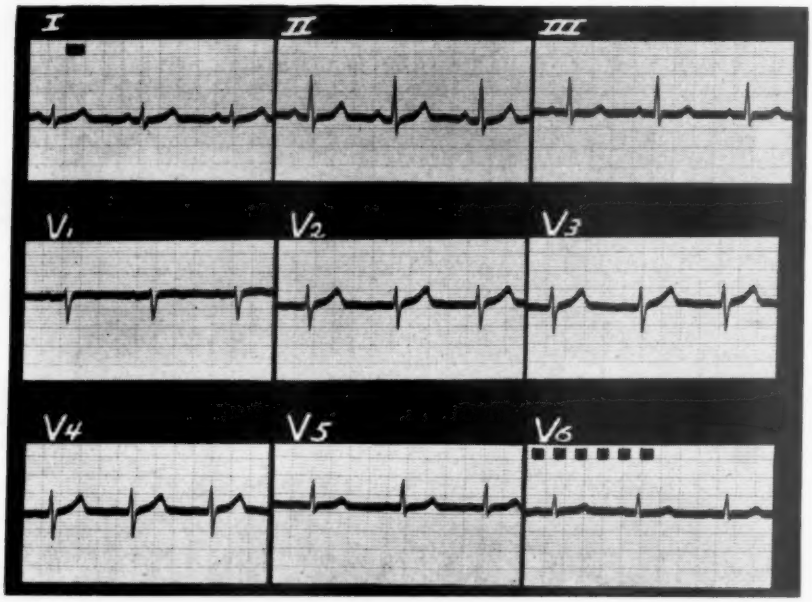

Fig. 6.—Normal electrocardiogram; heart in the semivertical position; normal A_{QRS}. Curve recorded thirty days following that shown in Fig. 5.

Three subjects were observed in whom electrocardiographic evidence of "ventricular hypertrophy" was present during the acute stage of rheumatic fever, while in subsequent curves, recorded after subsidence of the acute symptoms, the tracings were normal.

ELECTROCARDIOGRAMS OF UNUSUAL FORM

Fig. 7 is the electrocardiogram recorded from a 6-year-old white girl following five years of repeated attacks of rheumatic fever. Examination revealed harsh diastolic mitral and harsh systolic pulmonary and mitral murmurs, with both physical and roentgenographic evidence of moderate cardiac enlargement. The electrocardiogram shows a broad S in Lead I.[10] All standard precordial leads, including V_7 and V_8, present an initial R followed by a broad S, and the chief downstroke is early in the QRS interval. Unipolar leads recorded from the right hemithorax show that the downstroke of R occurs at the end of the QRS interval (see V_5', V_6', and V_7'). Two R deflections are present at V_E and V_F. These findings are diagnostic of incomplete right bundle branch block. The heart is in the horizontal position and counterclockwise rotation of A_{QRS} is present.

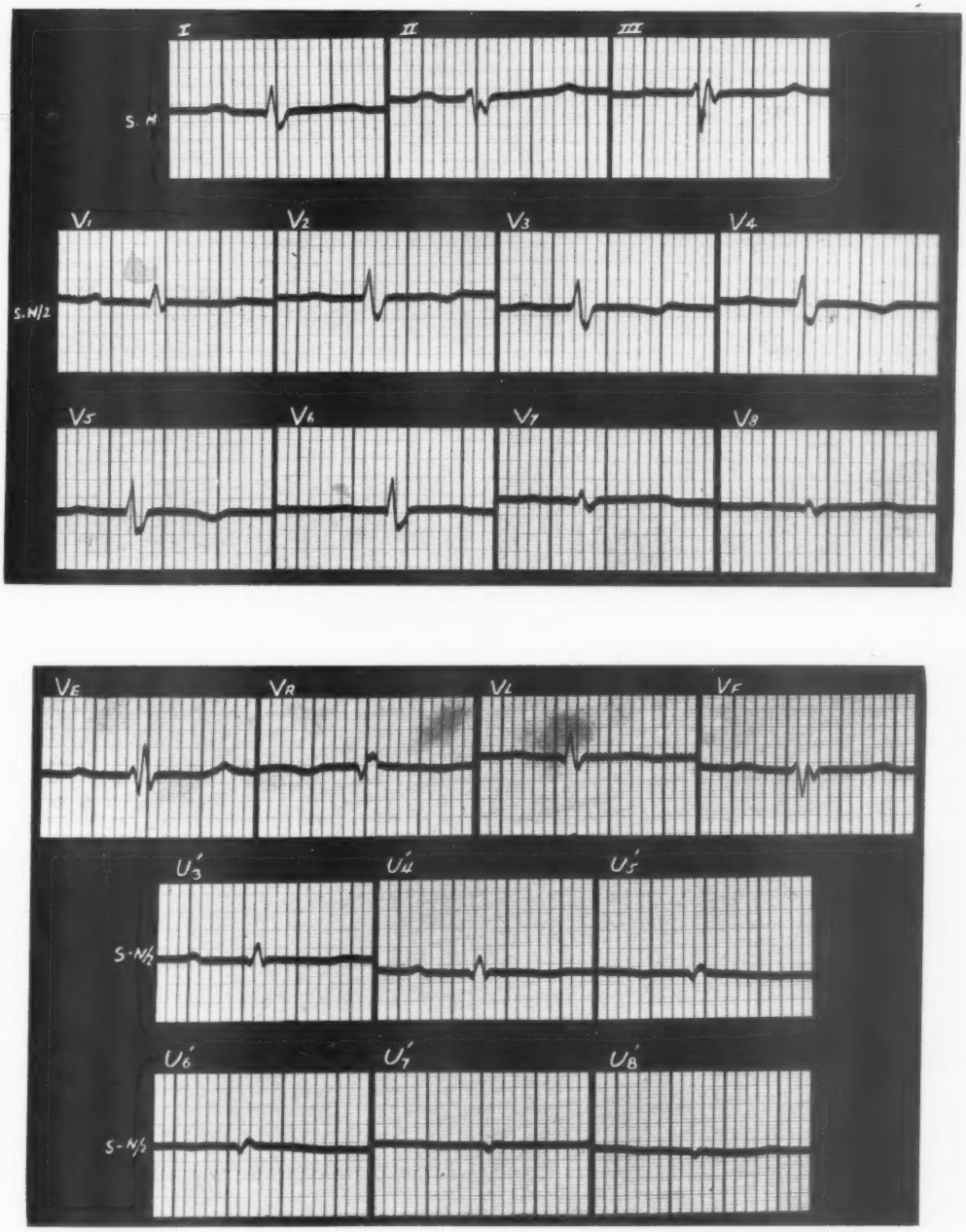

Fig. 7.—Child 6 years of age. Incomplete right bundle branch block; heart in the horizontal position; counterclockwise rotation of A_{QRS}. Precordial leads V_1 through V_8 are from the left side of the precordium. V_E is the unipolar lead from the midepigastric region. V_R, V_L, and V_F are unipolar leads from the extremities indicated by subscript. V'_3, V'_4, V'_5, V'_6, V'_7, and V'_8 are unipolar leads recorded from the right hemithorax at positions symmetrical with the standard precordial leads of corresponding subscript. All chest leads are recorded at one-half normal standardization.

It is interesting to note that all of the standard precordial leads recorded from this subject are from that part of the precordium to which the free wall of the left ventricle transmits its potential variations. The free wall of the right ventricle is on the diaphragm and transmits its potential variations to the lateral and posterior portion of the right hemithorax, to the epigastrium, and to the left leg.

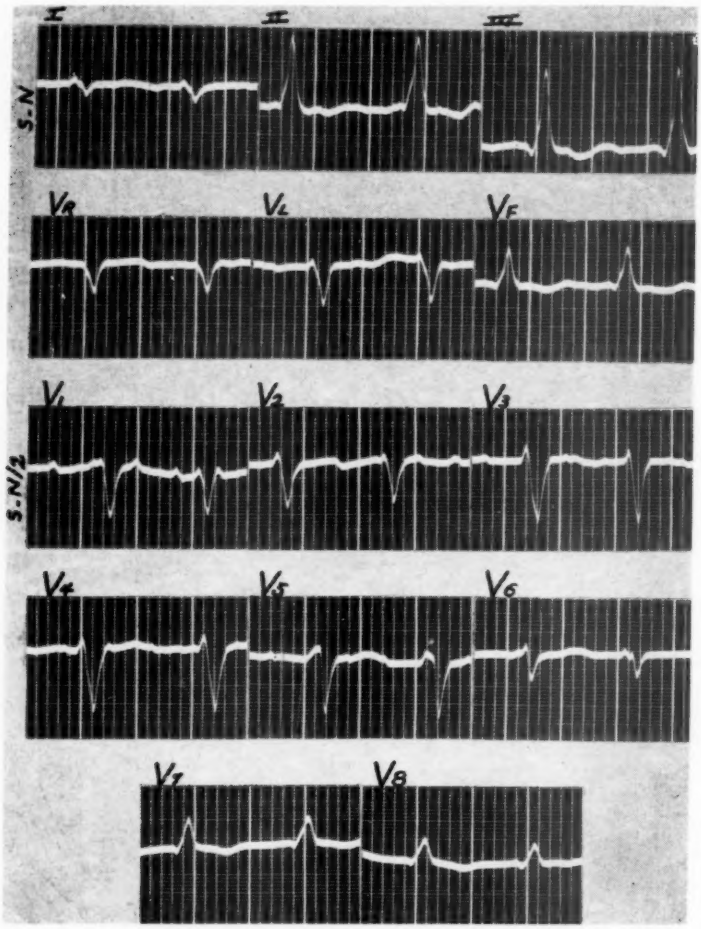

Fig. 8.—Child 12 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of A_{QRS}. Auricular fibrillation with rapid ventricular rate. Precordial leads V_1 through V_6 are from the right side of the precordium. Transition occurs between V_6 and V_7. V_7 and V_8 are from the left side of the precordium. Chest leads recorded at one-half normal standardization.

Fig. 8 is the electrocardiogram recorded from a 12-year-old white boy 7 years of age following an initial attack of rheumatic fever and three years following the onset of auricular fibrillation and myocardial decompensation. Examination revealed harsh mitral systolic and diastolic murmurs which completely obliter-

ated the first heart sound, and both physical and roentgenographic evidence of marked cardiac enlargement were present. The electrocardiogram shows a small R and prominent S in precordial leads V_1 through V_6 from the right side of the precordium, with a prominent R at V_7 and V_8 from the left side of the precordium. Unipolar extremity leads show deflections at the left shoulder (V_L) which resemble those from the right side of the precordium and deflections at the left leg (V_F) which resemble those of the left side of the precordium. These changes are diagnostic of left ventricular hypertrophy, heart in the vertical position, and clockwise rotation of A_{QRS}. Auricular fibrillation with rapid ventricular rate is also present.

It is of interest to note that all standard precordial leads, V_1 through V_6, recorded from this subject display potential variations which are transmitted from the right ventricle; the transition zone occurs between V_6 and V_7; V_7 and V_8 show potential variations transmitted from the left ventricular surface. Left ventricular hypertrophy is present, notwithstanding the fact that the patient has presented a clinical picture of mitral stenosis for several years.

A comparison of these findings with those of Fig. 7 reveals that the potential variations of the surface of either the left or of the right ventricle may be transmitted to that region of the precordium examined by Leads V_1 through V_6, depending upon the electrical position of the heart.

DISCUSSION

It would appear that left ventricular hypertrophy occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy. This, we feel, is based on the tendency of rheumatic myocarditis to involve predominantly the walls of the left ventricle.

As pointed out by Wilson and co-workers,[9] left ventricular hypertrophy in an electrically vertical heart produces clockwise rotation of the manifest mean electrical axis (A_{QRS}). Since the vertical and semivertical electrical positions are the most common in the age group of patients studied, it follows that a large number should show right axis deviation in the limb leads with evidence of left ventricular hypertrophy in the precordial leads.

Our observations confirm those of Taussig and Goldenberg[11] in that cardiac enlargement was not directly related to the endocardial (valvular) lesions and in that valvular lesions were not the prime factor in producing ventricular hypertrophy. In this connection, the electrocardiogram in Fig. 4 is one of many instances in which there is definite evidence of left ventricular hypertrophy, notwithstanding the fact that mitral stenosis was present. Many subjects studied (not included here) had clinical evidence of acute or chronic rheumatic heart disease unaccompanied by cardiac enlargement.

Thus far, we have used the term hypertrophy when the R and S deflections in the precordial leads exceeded the standard offered by Wilson and associates.[9-12] It should be pointed out, however, that cardiac dilatation, which produces a closer proximity of the ventricular and the thoracic walls, may, by

diminishing the distance from the exploring electrode to the accession wave, produce QRS deflections similar to those of hypertrophy. In subjects with electrocardiographic evidence of an initial increase in ventricular size and later a return to normal (Figs. 5 and 6), dilatation, rather than hypertrophy, probably predominates.

In Fig. 5, the T deflection at V_2 is low and notched, whereas a subsequent curve, Fig. 6, shows normal T deflections at all precordial leads. On frequent occasions the curves from subjects with acute rheumatic fever have shown abnormalities of RS-T and T in one or more of Leads V_1, V_2, and V_3. The current method of recording the limb leads and only one percordial lead will rarely reveal these changes.

Curves similar to that shown in Fig. 7, which almost certainly indicate incomplete right bundle branch block, may occasionally be confused with ventricular hypertrophy. A consideration of the standard six precordial leads, which show an R followed by a prominent S at all positions, might indicate right ventricular hypertrophy, incomplete right bundle branch block, or both if the heart is in the horizontal position, or, might indicate left ventricular hypertrophy, incomplete left bundle branch block, or both if the heart is in the vertical position. Furthermore, V_7 and V_8 do not settle the disputation. On the other hand, further examination of the limb leads with the view of estimating the form of V_F* leads directly to the proper diagnosis of incomplete right bundle branch block with the heart in the horizontal position. Added unipolar leads were utilized in order to confirm the diagnosis. Right ventricular hypertrophy cannot be excluded. A similar problem arises in connection with the diagnosis of hypertrophy from the electrocardiogram of Fig. 8.

SUMMARY

1. In the majority of subjects having rheumatic heart disease, left, rather than right, ventricular hypertrophy is responsible for clockwise or counterclockwise rotation of the manifest mean electrical axis (A_{QRS}) according to whether the electrical position of the heart is vertical or horizontal.

2. Typical electrocardiograms are presented illustrating "ventricular hypertrophy" in the various heart positions with associated diversions of A_{QRS}.

3. Myocardial, rather than endocardial (valvular), lesions play the primary role in producing ventricular enlargement.

4. Abnormalities of the final ventricular deflections in the first three precordial leads are of added value in the diagnosis of acute rheumatic fever.

5. Curves are presented which illustrate that standard positions V_1 through V_6 may, in certain instances, represent the potential variations from the surface of one ventricle, either the right or left, depending upon the position of the heart. In one such curve the proper interpretation of incomplete right bundle branch block was made only after a reconsideration of the limb leads, together with Leads V_1 through V_8.

*$V_F = \frac{LII + LIII}{3}$

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THE DURATION OF THE ELECTRICAL SYSTOLE (Q-T) IN ACUTE RHEUMATIC CARDITIS IN CHILDREN

LEO M. TARAN, M.D., AND NELLY SZILAGYI, M.D.
NEW YORK, N. Y.

THE clinical and pathologic relationship of carditis and rheumatic fever was demonstrated conclusively by Bouillard over one hundred years ago.[1] The prognosis in rheumatic disease, however, was based almost entirely upon the state of the valves until about fifty years ago, when the function of the heart muscle came to be studied in detail. And as late as 1924, Cohn and Swift[2] stated that it was not possible to say during the course of the acute stage of rheumatic fever, "whether heart disease is likely to be established." They were of the opinion that long periods of time were often required to pass after the acute episode before the diagnosis of heart disease became apparent.

In recent years the scene of interest has changed from the study of valvular damage to that of acute rheumatic carditis. It has become apparent to students of rheumatic fever in children that carditis is the most frequent manifestation of rheumatic fever and is most often insidious and subclinical.[3] From the diagnostic, prognostic, and therapeutic standpoints, acute rheumatic carditis is now recognized by most clinicians as being the most important manifestation of rheumatic fever.

But despite the great increase in the knowledge of the natural history of rheumatic disease and its cardiac manifestations, no clear-cut diagnostic criteria have been forthcoming. No criteria have been established for arriving at a judgment as to when rheumatic carditis is present, even in the case of obvious affection of the cardiac valves. The laboratory aids in diagnosis of rheumatic fever currently used have been disappointing in determining when the rheumatic inflammatory process in the heart muscle has begun or has ceased.[4]

In recent years, this field has been extensively yet inconclusively explored with the aid of the electrocardiograph. Considerable difference of opinion, however, exists with regard to the frequency of electrocardiographic abnormalities in patients suffering from acute rheumatic disease. The percentage incidence of electrocardiographic abnormalities ranges from 22 to 100 per cent in various studies. Of the fourteen most extensive reports up to 1941, one-half agree that abnormalities significant of involvement of the heart are found in 90 per cent or more of patients with rheumatic disease when frequent cardio-

From the St. Francis Sanatorium for Cardiac Children, Roslyn, L. I., New York.
Received for publication May 13, 1946.

graphic tracings are taken.[5] The most frequent abnormal finding is a prolongation of the auriculoventricular (P-R) conduction time.

The addition of precordial leads has increased the incidence of abnormal electrocardiographic findings in rheumatic fever. Lead IV was found of clinical value as an aid in the recognition of myocardial involvement in rheumatic fever; successive changes were interpreted as showing that the cardiac lesions were not in a quiescent state.[6] Convincing evidence has been reported showing that abnormal precordial leads are found with greater frequency than abnormal limb leads in children with active rheumatic disease.[7]

A critical review of the literature on electrocardiography in rheumatic fever emphasizes the fact that the electrocardiogram cannot be used as a specific diagnostic test for rheumatic carditis. The evidence presented is, in the main, of three sorts: (1) the duration of the A-V conduction time is increased, though not always; (2) there is frequent alteration in the ventricular complex, either the QRS, the S-T segment, or the T wave; (3) occurrence of irregularities in cardiac rhythm. It is pointed out that most electrocardiographic findings are transient and bear no clear-cut relationship to the clinical findings. Some alterations become fixed and cannot, therefore, be used as criteria for active carditis. Most electrocardiographic abnormalities described demonstrate evidence of temporary ischemia or permanent scar formation of the cardiac muscle. These findings seem to point to an inadvertent attempt to correlate electrocardiographic findings with the histopathology known to exist in rheumatic myocarditis. Few studies take into clear account the pathologic physiology mirrored in the cardiogram in the acutely inflamed heart muscle.

Physiologists have always contended that disturbance in time relationship of systole and diastole is a manifestation of impairment of the functional integrity of the myocardium. Wiggers and Clough[8] found consistently that the period of systole was of longer duration in functional cardiac disorders. They made the observation that when more blood returns to the ventricle, it responds by expelling more blood not only by a greater number of ejection periods, but also by a greater relative duration of each systole. Katz[9] has stated that the duration of systole in the diseased heart as compared with the normal heart would give a method of determining the functional integrity of the myocardium. Bazette[10] concluded from his evidence that the duration of systole in the abnormal heart may prove a measure of dilatation.

There is a wide difference of opinion, however, among physiologists and clinicians regarding the clinical importance of the measurement of the duration of the electrical systole (Q-T). Katz[11] has stated that "there is little practical value in measuring the duration of electrical systole." Ashman and Hull[12] on the other hand, believe that the measurement of the electrical systole may give valuable information regarding the degree to which the myocardium is being affected in diphtheria or in acute rheumatic carditis. Cheer[13] presented evidence to show that the electrical systole is greatly increased in heart failure irrespective of etiology and proposed the concept that an increased electrical systole may indicate a disturbance in cardiodynamics which might well be formed before clinical

evidence of failure is available. Tung[14] showed that the measurement of electrical systole may be used in the differentiation of pericardial effusion with heart failure from acute dilatation with failure; the Q-T interval is prolonged in the latter instance. Drawe and associates[15] found that the Q-T interval is definitely prolonged in about 25 per cent of the children with rheumatic disease whom they observed.

On the other hand, White and Mudd[16] concluded from an extensive study that the duration of the Q-T interval is apparently of little or no clinical value. They found no prolongation in patients with structural cardiac defects. In functional cardiac disturbances they found a prolonged Q-T interval only in paroxysmal tachycardias or disorders causing a marked widening of the QRS complex. Dock[17] stated that the duration of the Q-T interval is not a satisfactory index of cardiac function since only one-third of patients with failing hearts have systoles longer than the maximum found in normal subjects of the same sex and since the duration of the Q-T interval is the same in hypertensive patients with left ventricular preponderance without failure as in those who are badly decompensated.

It is clear, therefore, that while physiologists are in agreement that the prolongation of the duration of systole is significant of a disturbance in the functional integrity of the myocardium, clinically, insufficient evidence has been brought forth to support this physiologic concept. This discordance of opinion may be explained in part by the fact that the study of the component parts of the cardiac cycle have not been closely investigated in hearts showing an acute impairment of myocardial function but rather in cardiac conditions of long standing in which functional compensation has already been established at a given level of cardiac reserve. The study of children suffering from acute rheumatic carditis offers the opportunity to investigate the sequence of events in the cardiac cycle in a heart whose integrity is being actively impaired. On physiologic grounds, the duration of systole, both absolute and relative to diastole, in such hearts should be significantly disturbed. With this in mind, the following study was made.

PATIENTS STUDIED

A group of one hundred boys and girls from 7 to 14 years of age were studied under controlled conditions at the St. Francis Sanatorium for Cardiac Children. Fifty of these were observed during an episode of acute carditis* and for many months following rheumatic activity. The majority of the "active" group of cases were observed from the onset of carditis. A few were studied during a severe fulminating bout of pancarditis following a period of mild rheumatic activity. The other fifty boys and girls were observed during many months of quiescent rheumatic disease. The rheumatic disease in the majority of these had been quiescent for a minimum of twelve months prior to the period of observation;

*Only those children who presented both clinical and laboratory evidence of rheumatic carditis were included in this group.

in none, for less than six months. No intercurrent infections were observed during the study period in this group of children.

The age distribution in both "active" and "inactive" groups was practically the same. No significant difference in the extent of valvular involvement and the incidence and degree of cardiac enlargement was noted in the two groups. Children having auricular fibrillation or paroxysms of auricular or ventricular tachycardia were not included in this study. Those having marked intraventricular conduction disturbances were excluded from this investigation.

During the time that this study was in progress, none of the children received digitalis, salicylates, mercurials, or any form of intravenous therapy. Those who had received digitalis less than thirty days prior to the period of observation are not included in this study. All "inactive" children were ambulatory and participated in normal childhood activities. The "active" group were at complete bed rest during the entire period of rheumatic activity.

METHOD OF STUDY

Frequent electrocardiograms were made. These included the standard limb leads and three precordial leads (CF_2, CF_4, and CF_6). All electrocardiograms were taken with the patient in the recumbent position. The ambulatory patients were given a short rest period before tracings were taken. Clinical examination of the patient and pertinent laboratory tests were done at about the same time as the electrocardiograms were taken.

The Q-T and T-Q intervals were measured with the aid of a magnifying glass. Measurements were done in all leads and recorded. A minimum of twelve successive cycles were measured and the mean calculated. The duration of the Q-T was corrected for rate according to Bazette's formula.* The cardiac cycles used in the calculations were those used in measuring the actual Q-T interval.

All evaluations of the degree of rheumatic carditis in the "active" group were made without knowledge of the electrocardiographic measurements at the time of assessment. Likewise, the observation of the "inactive" group of children for rheumatic activity was done without the aid of the electrocardiograms.

RESULTS

Duration of Electrical Systole (Q-T).—Table I shows that the actual and corrected Q-T intervals are significantly longer in patients with acute carditis than in those with quiescent rheumatic disease. The average Q-Tc† for the "active" cases was 0.4374 second, as compared with 0.3924 second for the quies-

*The duration of the Q-T interval varies greatly with the length of the cardiac cycle. Consequently, in order to know whether a given Q-T is of normal length or not, one must know the normal length for the particular rate. This is expressed by Bazette's formula:

$$\text{Q-T corrected} = \frac{\text{Q-T interval in seconds}}{\sqrt{\text{Cardiac cycle in seconds}}}$$

†The corrected Q-T will be referred to here as Q-Tc.

TABLE I. DURATION OF ELECTRICAL SYSTOLE, BOTH ABSOLUTE AND RELATIVE TO DIASTOLE, IN FIFTY PATIENTS WITH ACUTE RHEUMATIC CARDITIS AND IN FIFTY PATIENTS WITH QUIESCENT RHEUMATIC FEVER

ACUTE CASES				QUIESCENT CASES			
RATE	Q-T	Q-Tc*	Q-T / T-Q	RATE	Q-T	Q-Tc	Q-T / T-Q
80	0.4036	0.466	1.13	72	0.3640	0.397	0.78
84	0.3800	0.449	1.16	72	0.3584	0.392	0.76
86	0.3760	0.445	1.19	72	0.3440	0.376	0.70
86	0.3580	0.423	1.05	74	0.3280	0.372	0.72
86	0.3864	0.457	1.22	76	0.3448	0.390	0.77
87	0.3660	0.436	1.14	76	0.3610	0.402	0.83
87	0.3720	0.447	1.16	77	0.3400	0.386	0.77
89	0.3520	0.428	1.08	77	0.3448	0.387	0.79
93	0.3480	0.435	1.17	79	0.3408	0.391	0.80
94	0.3484	0.435	1.20	79	0.3384	0.389	0.80
95	0.3620	0.455	1.32	79	0.3416	0.391	0.82
97	0.3424	0.434	1.26	80	0.3420	0.395	0.88
97	0.3340	0.425	1.15	81	0.3376	0.392	0.84
98	0.3292	0.423	1.14	81	0.3448	0.399	0.88
98	0.3484	0.445	1.14	81	0.3412	0.396	0.87
101	0.3392	0.438	1.34	82	0.3388	0.391	0.87
102	0.3428	0.444	1.41	82	0.3332	0.389	0.82
102	0.3280	0.426	1.17	83	0.3200	0.376	0.80
105	0.3400	0.444	1.46	83	0.3324	0.391	0.90
105	0.3200	0.421	1.22	83	0.3460	0.405	0.91
107	0.3400	0.450	1.54	85	0.3352	0.398	0.95
107	0.3244	0.433	1.38	85	0.3264	0.387	0.85
108	0.3472	0.466	1.67	86	0.3264	0.389	0.97
108	0.3192	0.428	1.34	86	0.3380	0.402	0.93
111	0.3150	0.428	1.36	87	0.3240	0.391	1.00
111	0.3200	0.436	1.45	87	0.3400	0.408	0.96
111	0.3192	0.435	1.45	87	0.3264	0.392	0.89
113	0.3212	0.443	1.57	87	0.3312	0.398	0.91
113	0.3144	0.432	1.31	88	0.3200	0.387	0.80
113	0.3412	0.466	1.80	88	0.3240	0.393	0.90
115	0.3028	0.420	1.38	89	0.3200	0.390	0.91
116	0.3200	0.446	1.63	90	0.3250	0.405	0.95
118	0.3212	0.451	1.72	90	0.3180	0.390	0.92
118	0.3100	0.436	1.64	92	0.3360	0.400	1.05
119	0.2984	0.419	1.45	93	0.3032	0.379	0.92
120	0.2920	0.413	1.39	95	0.3064	0.385	0.92
122	0.2920	0.415	1.45	95	0.3132	0.394	0.97
123	0.2920	0.418	1.49	96	0.2948	0.375	0.93
124	0.3200	0.455	1.95	101	0.3164	0.405	1.13
125	0.3024	0.436	1.69	101	0.3064	0.394	1.06
126	0.2960	0.427	1.64	102	0.3024	0.390	1.02
128	0.2912	0.425	1.63	102	0.3052	0.394	1.08
129	0.3000	0.438	1.82	102	0.3036	0.391	1.07
129	0.2924	0.429	1.62	103	0.3084	0.400	1.13
129	0.3016	0.441	1.86	103	0.3068	0.398	1.12
133	0.2920	0.437	1.91	105	0.3100	0.403	1.19
134	0.3144	0.471	1.99	105	0.2724	0.361	0.92
136	0.2864	0.430	1.55	107	0.3004	0.401	1.14
150	0.2800	0.443	2.33	113	0.2840	0.390	1.17
154	0.2628	0.430	2.04	117	0.2912	0.405	1.32
Av. 114	0.3261	0.4374	1.463	88.7	0.3276	0.3924	0.9278

*Q-Tc refers to the corrected Q-T interval.

cent cases. Since the average duration of the Q-T interval in normal children is said to be 0.325 second[18] and the upper limit of the normal Q-Tc for children is 0.405 second,[12] it is apparent from our observation that the duration of systole of practically all children with quiescent rheumatic disease is within normal limits. On the other hand, all those with acute carditis have a systole significantly longer than the upper limit of normal. The shortest Q-Tc in this group was found to be moderately longer than the longest Q-Tc for the quiescent group.

Relation of Electrical Systole to Cardiac Rate.—It is well known that systole shortens appreciably with increasing cardiac rate. It is also widely appreciated that the cardiac rate in acute carditis is higher than in quiescent hearts. It is thus of great significance to find that the duration of systole is markedly longer in acute carditis than in the quiescent heart irrespective of cardiac rate. It will be noted on the distribution chart (Fig. 1) that all acute hearts have long Q-Tc intervals at any cardiac rate, and likewise that the quiescent hearts have short systoles Q-Tc at any cardiac rate. In addition, it is obvious that the duration of systole in acute cases is apparently uninfluenced by cardiac rate.

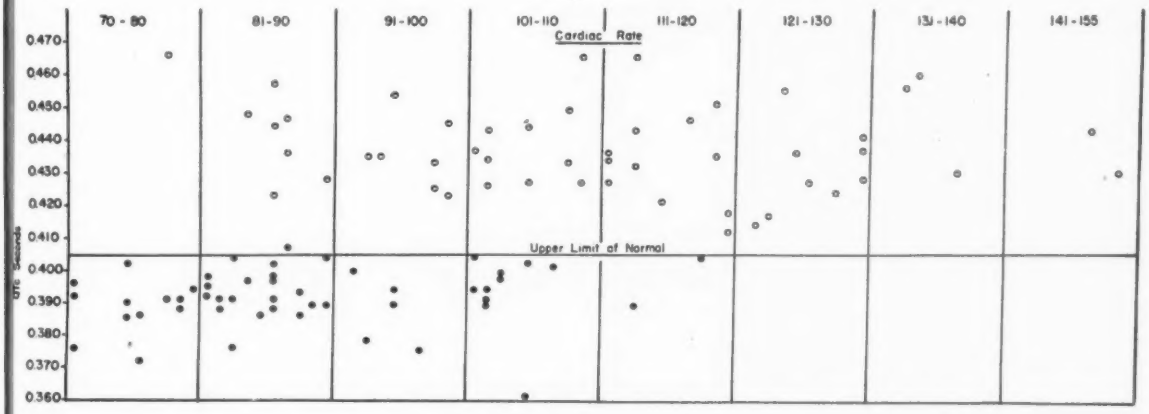

Fig. 1.—Duration of electrical systole in children with active and quiescent rheumatic fever in relation to cardiac rate. On this chart, fifty "active" and fifty "inactive" cases are distributed according to the Q-Tc of the patients at the time of observation and the cardiac rate at the same time.

The Ratio of Systole to Diastole $\frac{(Q\text{-}T)}{(T\text{-}Q)}$.—The physiologic principle that in normal hearts diastole is longer than systole is common knowledge. The ratio of the duration of systole to the duration of diastole is of the order of less than 1 up to the cardiac rate of 100. Table I shows that the $\frac{\text{Q-T}}{\text{T-Q}}$ quotient in the quiescent group of children is well within normal limits; that is, less than 1. Quotients slightly higher than 1 are found only among those with a cardiac rate above 100. Patients with acute carditis, on the other hand, have a markedly increased

$\frac{Q\text{-}T}{T\text{-}Q}$ quotient. The average quotient for this group is 1.463. None of these children have a quotient of less than 1 and a few have a quotient of more than 2.

It is clear from these observations that the duration of systole, both absolute and relative to diastole, is significantly longer in patients with acute carditis than in patients with quiescent rheumatic disease.

Relationship of $\frac{Q\text{-}T}{T\text{-}Q}$ *Quotient to Cardiac Rate.*—The physiologic principle that systole shortens less rapidly than diastole with increasing cardiac rate is also well known. This means that the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient becomes greater with increasing cardiac rate. Our observation would seem to show that in patients with acute carditis the prolongation of systole relative to diastole follows this physiologic principle but at a significantly higher rate level; the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient

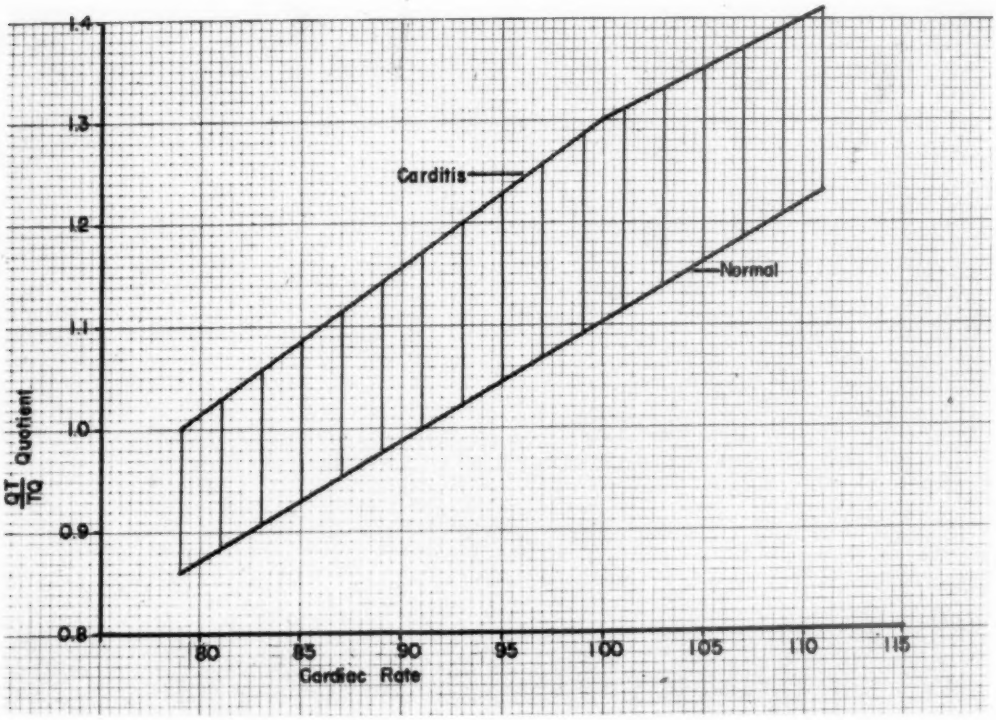

Fig. 2.—This represents the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient of a child with acute carditis at different levels of cardiac rate. The line labeled normal represents the calculated quotients at corresponding rates on the basis of the upper limit of normal Q-Tc of 0.405 second. The severity of carditis as judged by clinical observation of the patient was about the same at each rate. The parallelism of the two lines demonstrates that the prolongation of systole relative to diastole in acute carditis, as compared to normal, is uninfluenced by cardiac rate.

becomes greater with an increase in cardiac rate, but at a much higher heart rate than in children with quiescent hearts. Furthermore, in the presence of active carditis, this increasing quotient runs parallel to that found in children with normal (or quiescent) hearts provided the degree of carditis, as judged by the clinical course, is about the same at the various cardiac rates (Fig. 2).

It is clear from this observation that the difference in the magnitudes of the quotients in those with acute and quiescent hearts is not a function of cardiac rate. This would seem to predicate another factor which is responsible for the marked prolongation of systole relative to diastole that is found in acute carditis.

Relationship of $\frac{Q\text{-}T}{T\text{-}Q}$ *Quotient to Severity of Carditis.**—Examination of Table II shows that the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient increases significantly with increase in severity of carditis. The average $\frac{Q\text{-}T}{T\text{-}Q}$ quotient in the group of children with the mildest grade of carditis (1 plus) was 1.257 as compared with 1.825 in the group with the severest form of carditis (4 plus). Table II also shows that the difference between the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient of acute cases and that of the calculated quotient for comparable cardiac rate rises with the increase in severity of the carditis. That the

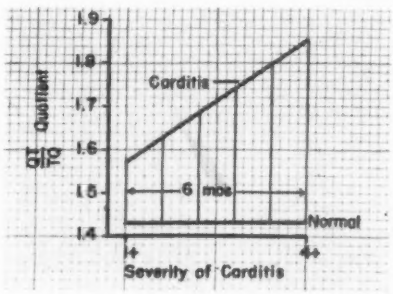

Fig. 3.—This illustrates the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient of a child who was admitted with mildly "active" rheumatic disease but whose activity increased in severity over a period of six months. The quotient 1.85 was calculated from the cardiogram taken shortly before the child died of acute pancarditis. The cardiac rate at the highest and the lowest quotients was the same, 125. The line labeled normal represents the calculated quotient at a rate of 125 with a Q-Tc of 0.405 second.

*For many years patients at St. Francis Sanatorium suffering from rheumatic carditis have been graded according to the following criteria:

1 plus severity: Patients who present laboratory evidence of rheumatic activity and, in addition, present the clinical criteria of cardiac involvement; that is, changing heart sounds and murmurs, labile cardiac rate, and fatigability.

2 plus severity: Patients who, in addition to the foregoing findings, show definite cardiographic evidence of conduction disturbance or/and changes in the ventricular complexes.

3 plus severity: Patients, who, in addition to the foregoing, present a tumultuous heart with moderate symptoms of impaired cardiac reserve.

4 plus severity: Patients with acute pancarditis.

TABLE II. DURATION OF SYSTOLE BOTH ABSOLUTE AND RELATIVE TO DIASTOLE IN RELATION TO DEGREE OF SEVERITY OF CARDITIS

	1	2	3	4	5	6	7
	RATE	Q-T	Q-T UPPER LIMIT OF NORMAL	Q-Tc	$\frac{Q\text{-}T}{T\text{-}Q}$	$\frac{Q\text{-}T}{T\text{-}Q}$ UPPER LIMIT OF MORNAL	DIFFERENCE CLMS 5-6
				Carditis 1 Plus Severity			
	102	0.3280	0.3116	0.426	1.17	1.130	0.040
	113	0.3144	0.2950	0.432	1.31	1.250	0.060
	98	0.3484	0.3170	0.435	1.14	1.068	0.070
	97	0.3340	0.3200	0.425	1.15	1.060	0.090
	123	0.2920	0.2846	0.418	1.49	1.390	0.100
	86	0.3580	0.3390	0.423	1.05	0.940	0.110
	115	0.3028	0.2920	0.420	1.39	1.280	0.110
	111	0.3150	0.2980	0.428	1.36	1.230	0.130
Av.	105	0.3240	0.3071	0.4252	1.257	1.168	0.0880
				Carditis 2 Plus Severity			
	93	0.3480	0.3230	0.435	1.17	0.990	0.180
	94	0.3484	0.3227	0.435	1.20	1.010	0.190
	126	0.2960	0.2814	0.427	1.64	1.450	0.190
	105	0.3200	0.3080	0.421	1.37	1.170	0.200
	107	0.3244	0.3045	0.433	1.39	1.190	0.200
	87	0.3720	0.3370	0.447	1.16	0.950	0.210
	111	0.3192	0.2980	0.435	1.45	1.230	0.220
	111	0.3200	0.2980	0.436	1.45	1.230	0.220
	101	0.3392	0.3130	0.438	1.34	1.110	0.230
	84	0.3800	0.3420	0.449	1.16	0.920	0.240
Av.	102	0.3367	0.3127	0.4356	1.333	1.125	0.2080
				Carditis 3 Plus Severity			
	125	0.3024	0.2826	0.436	1.69	1.430	0.260
	86	0.3864	0.3398	0.457	1.22	0.940	0.280
	95	0.3620	0.3214	0.455	1.32	1.030	0.290
	105	0.3400	0.3080	0.444	1.46	1.170	0.290
	102	0.3488	0.3116	0.453	1.45	1.130	0.320
	113	0.3212	0.2950	0.443	1.57	1.250	0.320
	107	0.3400	0.3045	0.450	1.54	1.190	0.350
Av.	119	0.3429	0.3088	0.4482	1.464	1.157	0.3014
				Carditis 4 Plus Severity			
	129	0.3016	0.2780	0.441	1.86	1.460	0.400
	118	0.3212	0.2888	0.451	1.72	1.310	0.410
	134	0.3144	0.2700	0.471	1.99	1.550	0.440
	108	0.3472	0.3020	0.466	1.67	1.194	0.476
	113	0.3412	0.2950	0.466	1.76	1.230	0.530
	124	0.3200	0.2837	0.455	1.95	1.400	0.550
Av.	120	0.3242	0.2862	0.4583	1.825	1.357	0.5676

1, Cardiac rate; 2, measured Q-T interval; 3, Q-T interval calculated on basis of 0.405 (upper limit of normal); 4, corrected Q-T interval; 5, quotient calculated from measured Q-T interval; 6, quotient calculated from column 3.

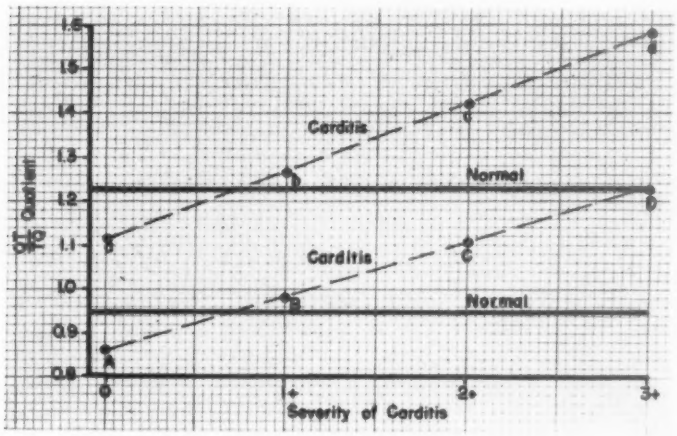

Fig. 4.—This represents the $\frac{Q\text{-}T}{T\text{-}Q}$ quotients of eight rheumatic children. *A* was quiescent with a cardiac rate of 86. *B*, *C*, and *D* had acute carditis with the same cardiac rate as *A*. Cases *a*, *b*, *c*, and *d* represent children with a cardiac rate of 111 but with a degree of carditis corresponding to that in *A*, *B*, *C*, and *D*.

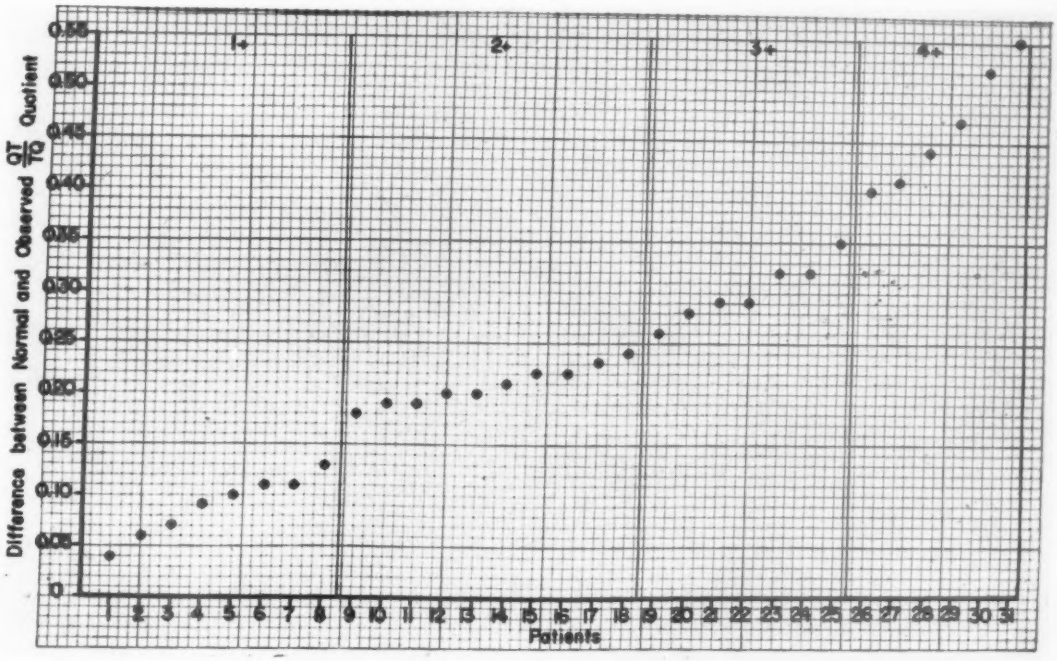

Fig. 5.—This represents the $\frac{Q\text{-}T}{T\text{-}Q}$ quotients of thirty-one patients with acute carditis. These were arranged on the graph in order of magnitude of the quotient. The ordinate represents the difference between the normal quotients for corresponding cardiac rates and the observed quotients of our patients. Patients 1 through 8 were diagnosed as having mild carditis, (1 plus); 9 through 18, a moderate carditis (2 plus); 19 through 25, a marked carditis (3 plus); 26 through 31, a severe pancarditis (4 plus).

increase in quotient is absolute and not influenced by rate is well illustrated in Figs. 3 and 4. This finding was common in all our patients with acute carditis when studied in this manner (Fig. 5). Furthermore it was observed that as the severity of carditis increases in the same patient, the $\frac{Q\text{-}T}{T\text{-}Q}$ quotient rises accordingly, and as carditis subsides, the reverse is the case. This is uninfluenced by cardiac rate (Figs. 6 and 7).

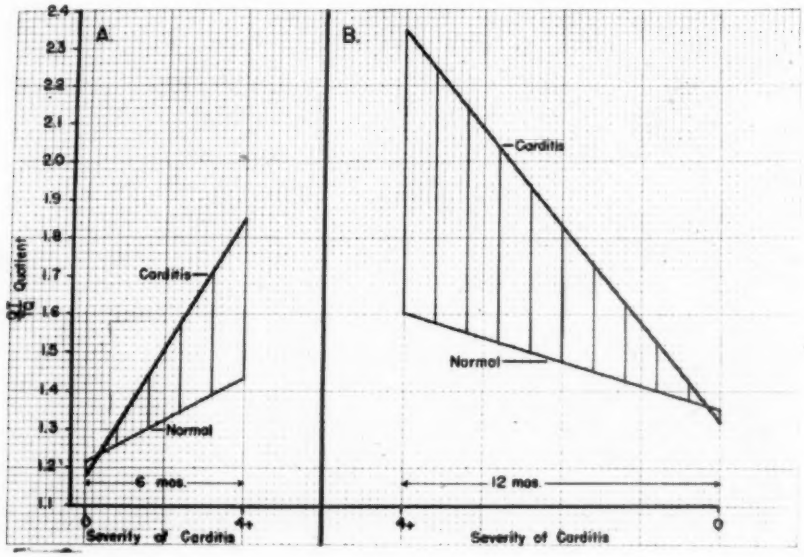

Fig. 6.—*A* represents a patient whose $\frac{Q\text{-}T}{T\text{-}Q}$ quotient was studied from quiescence to the end of a fulminating pancarditis. *B* represents a patient who was admitted with a severe carditis and recovered. The lines labeled normal represent a calculated quotient at corresponding cardiac rates with a maximum normal Q-Tc of 0.405 second.

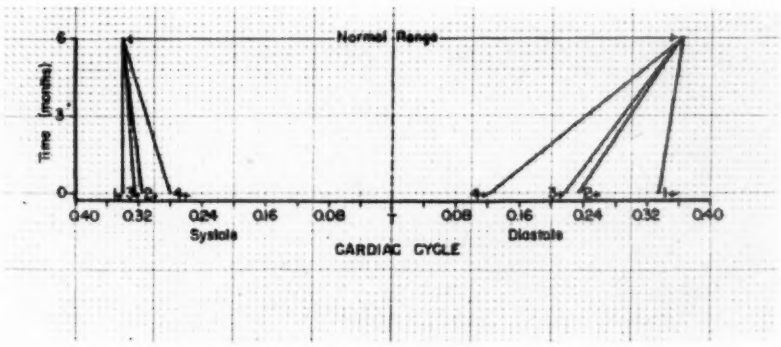

Fig. 7.—This chart represents the duration of systole relative to diastole of four patients with acute carditis of different degrees of severity. These were followed until quiescence, at which time they all had a Q-Tc of 0.400 and a rate of 86.

COMMENT

The diagnosis and evaluation of cardiac involvement during the course of the acute stage of rheumatic disease has been one of the trying problems in medicine for many years. In recent years much has been learned from electrocardiographic studies regarding the occurrence and extent of cardiac damage in rheumatic fever. Criteria for recognition and evaluation of impairment of the integrity of the heart muscle during the course of acute carditis, however, have not been forthcoming. The physiologic principle that the disturbance in the normal time sequence of events in the cardiac cycle is significant of an impaired heart muscle has not been fully explored by clinicians in the study of rheumatic carditis.

The observations presented in this paper seem to indicate that a distinct disturbance of cardiodynamics is present in acute carditis and that this disturbance is mirrored in the abnormal relationship of the duration of systole relative to diastole. The apparent inversion of the normal time sequence of events in the cardiac cycle is a constant finding in cases of acute carditis. In addition, we have found this abnormal sequence helpful in evaluating the degree of impairment of the functional integrity of the heart muscle. The degree of severity of carditis as measured by clinical observation of the patient and the extent of disturbance in the time relationship of systole relative to diastole run almost exactly parallel in our group of cases.

Our findings, furthermore, would seem to add a more direct method for studying the duration of rheumatic activity. Those patients who are considered to have subclinical rheumatic activity show a significant cardiodynamic disturbance. As long as this disturbance in the normal time sequence of events in the cardiac cycle is found, the presence of rheumatic activity should be suspected. Our experience with these children teaches that those who show an abnormal prolongation of the duration of systole relative to diastole do poorly when treatment is terminated even when all other laboratory criteria are normal. We are also impressed from these studies that few, if any, children having rheumatic disease escape active impairment of the integrity of the heart muscle during the course of the acute stage of the disease.

Finally, our observations point the way to a better evaluation of the effect of various forms of therapy used in acute carditis. Bed rest, salicylates, digitalis, diuretics, oxygen, and other forms of treatment now employed in acute carditis can be studied in relation to the extent and duration of acute cardiac involvement. These studies are now in progress.

SUMMARY AND CONCLUSIONS

1. One hundred boys and girls from 7 to 14 years of age were observed under controlled conditions—fifty during an attack of acute carditis and fifty during a long period of quiescence.

2. The duration of electrical systole (Q-T) both absolute and relative to diastole was studied in these children in relation to cardiac rate and severity of carditis.

3. The observation was made that the duration of electrical systole (Q-T) both absolute and relative to diastole is significantly prolonged in all cases of acute carditis.

4. This prolongation was found to be a function of the severity of the carditis and not of the cardiac rate.

5. It is postulated that this disturbance in the normal sequence of events in the cardiac cycle is characteristic of acute carditis and adds a valuable diagnostic criterion for the recognition of rheumatic carditis and an electrocardiographic method for following the progress of carditis.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH METHYL ALCOHOL POISONING

LIEUTENANT AUSTIN S. WEISBERGER AND LIEUTENANT JAMES A. MACLAUGHLIN
MEDICAL CORPS, UNITED STATES NAVAL RESERVE

THE toxicity, pathologic findings, and treatment of methyl alcohol poisoning are well known and have been reviewed by Voegtlin and Watts,[1] Jacobson, Russell, Grimm, and Fox[2] and Kaplan and Leverault.[3] Electrocardiographic changes, however, are not mentioned in these reviews, and a survey of the literature reveals only one case report[4] in which electrocardiographic changes were demonstrated. Furthermore, no mention of electrocardiographic abnormalities associated with wood alcohol poisoning is made in standard medical textbooks. The following report deals with eight cases of methyl alcohol poisoning in which electrocardiographic studies were undertaken.

CASE MATERIAL

Nine men accidentally ingested various quantities of methyl alcohol from an unmarked container under the assumption that it was grain alcohol. The alcohol was diluted approximately one part in three with water, and the amounts ingested varied from five to six large cupfuls to a few sips. The exact amounts ingested could not be ascertained accurately. All were admitted to the hospital two days later. One man died about forty-eight hours after drinking this mixture and one became blind. The others recovered entirely.

Headache, nausea, vomiting, blurring of vision, scotomas, weakness, myalgia, and lassitude were common complaints in all and existed in varying degrees of severity. Of the eight patients who survived, two appeared seriously ill on admission, one of the men being semicomatose. Two of the patients appeared mildly ill and the remainder had only minor complaints. Hyperpnea and râles in the lung bases were noted in three of the men and cyanosis in two. Otherwise the physical findings were not striking. Six patients had a positive test for acetone in the urine.

Treatment consisted of parenteral fluids, sodium bicarbonate by mouth, Ringer-lactate solution intravenously, and liver extract intramuscularly. Four of the patients received small doses of insulin with large amounts of glucose. The most seriously ill patients received plasma.

Electrocardiograms were taken twelve hours after admission, five days after treatment had been instituted, and again eleven days after admission.

RESULTS

Seven of the eight cases showed definite electrocardiographic changes which reverted toward normal following treatment (Table I). Five showed marked abnormalities and two showed changes of lesser degree. One man had a normal electrocardiogram except for slight prolongation of the Q-T interval. Electro-

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TABLE I. ELECTROCARDIOGRAPHIC FINDINGS AFTER INGESTION OF METHANOL

CASE	RELATIVE ESTIMATED AMOUNTS OF METHANOL INGESTED	CLINICAL APPEARANCE	ECG TWELVE HOURS AFTER ADMISSION	ECG FIVE DAYS AFTER TREATMENT	ECG ELEVEN DAYS AFTER TREATMENT
1	++++	Seriously ill	Low voltage T in Leads I and II; T_3 isoelectric	Increased voltage of T in Leads I, II, and III	No change from previous tracing
2	±	Appeared normal	Normal except for slight prolongation of Q-T interval	No change	No change from previous tracing
3	++++	Appeared normal	Low voltage T in Leads I, II, and III; T in CF_4 diphasic	Increased voltage of T in Leads I, II, and III; T in CF_4 no longer diphasic	Further increase in voltage of T in Leads II and III
4	+++	Appeared normal	Low voltage T in Leads I and II; T_3 diphasic	T_1 increased in voltage	T_2 increased in voltage
5	++	Appeared normal	Low voltage T in Leads I, II, III, and CF_4	Increased voltage T in Leads I, II, and CF_4; amplitude of T_3 decreased and QRS notched in CF_4	Further increase in voltage of T_2 and T_3; QRS no longer notched in CF_4
6	++++	Mildly ill	Record within normal limits; T_3 inverted	T_2 slightly increased in voltage; T_3 upright	Increased voltage of T_3
7	+++	Mildly ill	Low voltage T_1 and T_2	T_2 increased in voltage	Increased voltage of T_1 and T_2
8*	++++	Seriously ill	Low voltage T_1 and T_2	Increased voltage of T_1 and T_2; T_3 now inverted	Further increase in voltage of T_1 and T_2

*Developed amblyopia.

cardiograms taken eleven days after admission showed continuing changes in the same direction in six of the patients.

The most frequent finding was low voltage of the T waves in Leads I and II which reverted toward normal after treatment (Figs. 1 and 2). Increased voltage of the T waves in Lead III and in CF_4 following treatment were noted in several of the patients (Table I). Minor changes in the QRS complex also occurred. The Q-T interval as determined by the formula $K = \frac{QT^*}{\sqrt{RR}}$ was found to be slightly prolonged in four patients (Table II).

TABLE II. DURATION OF Q-T INTERVALS

CASE	BEFORE TREATMENT (SEC.)	FIVE DAYS AFTER TREATMENT (SEC.)	ELEVEN DAYS AFTER TREATMENT (SEC.)
1	.39	.39	.41
2	.40	.39	.40
3	.38	.38	.40
4	.39	.395	.39
5	.36	.37	.38
6	.37	.38	.38
7	.40	.40	.395
8	.36	.36	.36

COMMENT

The electrocardiographic changes which occurred in these patients are comparable to those found in the patient reported on by Merritt and Brown.[4] In their patient, however, a normal electrocardiogram was found on admission and changes did not occur until four days after the ingestion of the poison and twenty-four hours after treatment had been instituted. The findings in our patients were present about sixty hours after the men had partaken of the methyl alcohol.

Somewhat similar changes, including prolongation of the Q-T interval, were found by Bellet and Dyer[5] in seventeen patients with diabetic acidosis. However, here too, the electrocardiographic changes did not occur until twenty-four hours after treatment had been instituted. S-T segment depression also occurred in their patients but was not present in ours. Both Merritt and Brown[4] and Bellet and Dyer[5] attribute the electrocardiographic changes to delayed myocardial damage occurring as the result of acidosis.

The oxidation of methyl alcohol results in an acidosis due to the formation of formic acid and formaldehyde. Unfortunately, determinations of the carbon dioxide combining power were not available in these patients, but it is safe to

*Bazetts' formula corrected for Q-T interval. K is a constant. R-R is the cycle length.

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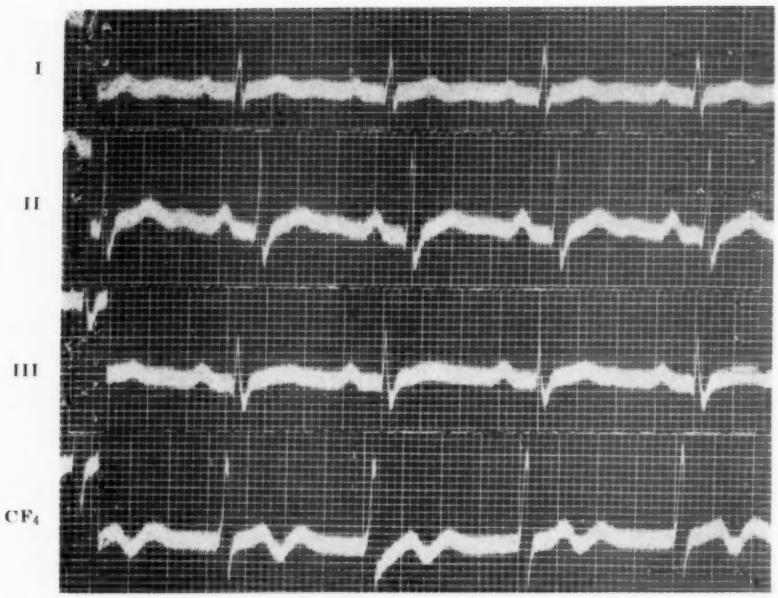

Fig. 1*A*.—Case 3. Electrocardiogram twelve hours after admission. Low voltage of T waves in Leads I, II, and III. T in CF_4 is slightly diphasic. Prominent U waves are present in CF_4.

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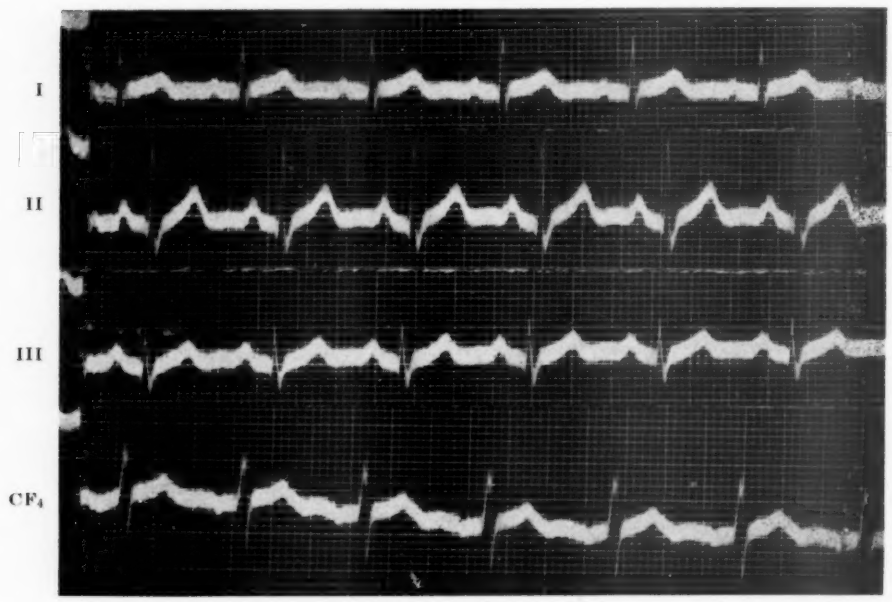

Fig. 1*B*.—Case 3. Electrocardiogram after treatment. T waves in Leads I, II, and III have increased in amplitude. T in CF_4 no longer diphasic.

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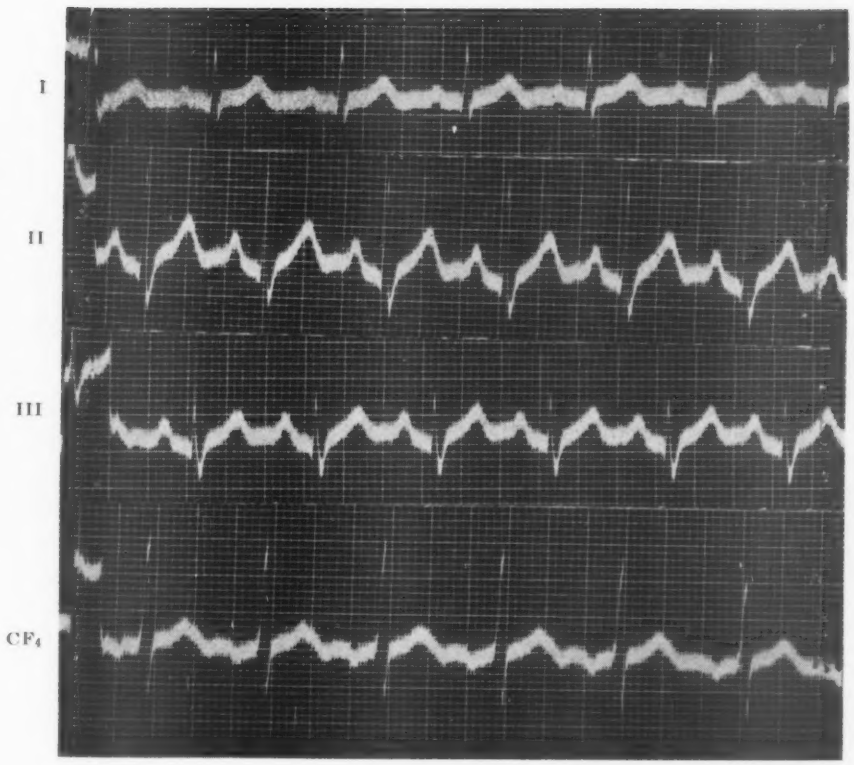

Fig. 1*C*.—Case 3. Electrocardiogram eleven days after treatment shows further increase in voltage of T waves in Leads II and III.

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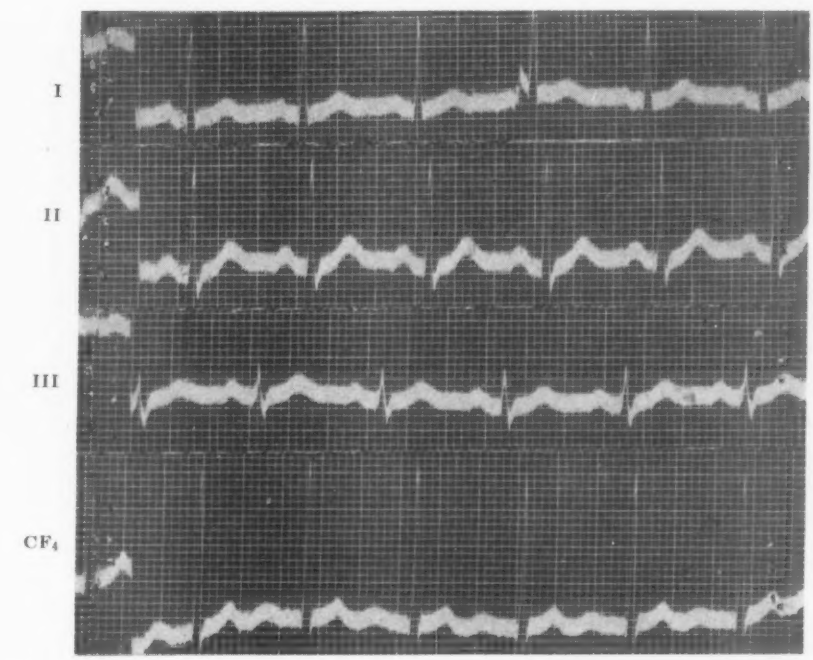

Fig. 2*A*.—Case 5. Electrocardiogram twelve hours after admission. Low voltage of T waves in Lead I and in CF_4.

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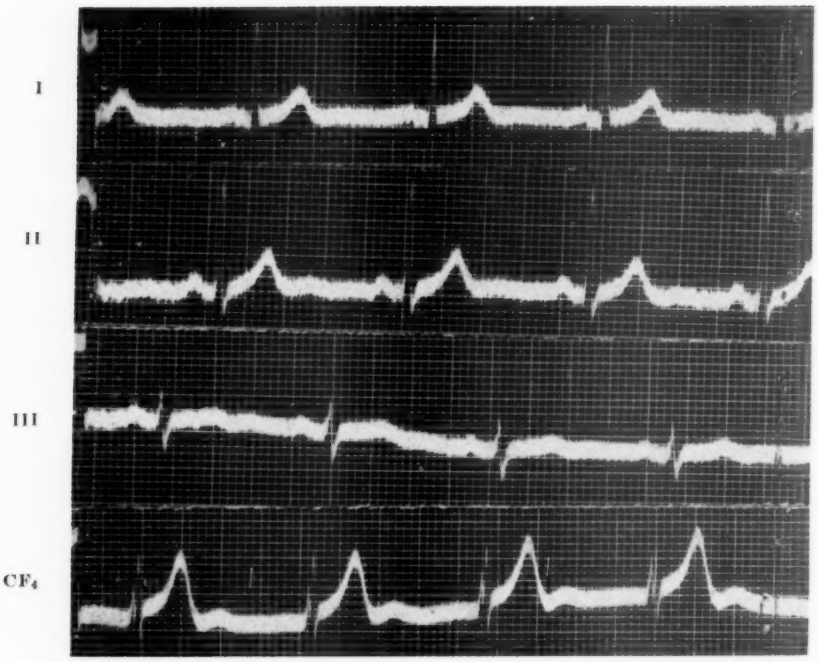

Fig. 2*B*.—Case 5. Electrocardiogram after treatment. Increased voltage of T waves in Leads I and II, and in CF_4. T_3 decreased in voltage and QRS notched in CF_4.

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Fig. 2*C*.—Case 5. Electrocardiogram taken eleven days after treatment shows further increase in voltage of T waves in Leads II and III. QRS complex no longer notched in CF_4.

assume that they were probably suffering from acidosis at the time of admission. However, methyl alcohol, formic acid, and formaldehyde are all toxic substances, per se, and the possibility of direct myocardial toxicity cannot be ruled out entirely.

No direct correlation could be drawn between the degree of electrocardiographic change and the estimated amount of methanol ingested. The patient (Case 2), however, who showed no change except slight prolongation of the Q-T interval, took the least amount of alcohol. It was the clinical impression that habituation to alcohol exerted a protective influence.

The Q-T intervals were found to be only slightly prolonged and were not significantly altered following treatment. No correlation could be drawn between the amount of electrocardiographic changes which occurred and the duration of the Q-T interval.

SUMMARY AND CONCLUSIONS

1. Electrocardiographic changes were found in seven of eight patients with methyl alcohol poisoning.
2. The most common finding was decrease in voltage of the T waves in Leads I and II.
3. Slight prolongation of the Q-T interval was present in four patients but did not appear to be significant.
4. The electrocardiograms reverted toward normal after treatment.
5. The cause of the electrocardiographic changes is not known but may be due to acidosis or to the direct effect of methyl alcohol or its metabolites on the myocardium.

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ATRIONODAL RHYTHM WITH VENTRICULAR BIGEMINY

Report of a Case With Unusual Mechanism

Julius S. Perelman, M.D., and Ralph Miller, M.D.
Newark, N. J.

RARELY a dominant atrionodal rhythm is complicated by ventricular bigeminy. This irregularity is of particular interest because of the wide variety of mechanisms by means of which the second beat of the pair might be linked with the first. The explanation for the coupling in some cases is obvious, in others obscure, and, in still others, entirely speculative. After a thorough search of the literature, the following list of mechanisms which might result in atrionodal bigeminy was compiled:

1. Atrionodal beats coupled with premature sinus,[1] auricular, nodal,[2] or ventricular[2] contractions
2. Reciprocal rhythm[3,4]
   A. With retrograde conduction to auricles
   B. With reciprocal pathway limited to A-V node [4,5]
3. Auricular parasystole with interference dissociation[6,7]
4. Nodal escape beats paired with sinus beats[8] (pseudoreciprocal rhythm[9])
   A. With sinus nodal pacemaker in normal location
   B. With sinus nodal pacemaker outside of normal location[10]
5. Nodal escape beats paired with auricular escape beats[6]
6. Nodal escape beats paired with nodal extrasystoles
   A. Without independent auricular rhythm[11]
   B. With independent auricular rhythm and interference dissociation[2]
7. Normal supraventricular beats interpolated upon a dominant A-V nodal rhythm[12,13]
8. A dominant A-V nodal rhythm, paired with sinus nodal or auricular beats, which are mechanically stimulated by the contracting ventricle[14]

In this paper we describe an unusual example of atrionodal rhythm with ventricular bigeminy which was characterized by the following rhythmic sequences: (1) ventricular complex of atrionodal origin; (2) antegrade, abnormal P wave; (3) normal, or aberrant, QRS complex. The coupling between the first ventricular beat and the auricular beat, or between the two ventricular beats, was fixed. Although we cannot explain the mechanism precisely, we believe the theoretical implications are of sufficient interest to warrant placing this case on record.

From the Cardiac Clinic of the Newark, N. J. Health Department.
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CASE REPORT

J. McN., a 56-year-old Negro woman, was first referred to the Cardiac Clinic in September, 1940, because of dyspnea, palpitation and substernal pain on exertion, and dizziness. She admitted a past history of syphilis, for which she had received adequate treatment from 1935 to 1938. The heart beat was regular, the rate 60 per minute, and the blood pressure was 160/90. The heart was enlarged moderately to the left, and a faint, harsh systolic murmur was audible over the aortic area.

She was again referred for study in August, 1944. Because of a history of dizziness, staggering, and syncope, and the presence of a bradycardia, it was suspected that she might be suffering from the Adams-Stokes syndrome. The physical examination revealed no essential change, except that her blood pressure had risen to 175/120. No disturbances of rhythm or conduction were demonstrated by the electrocardiogram.

It was not until one year later, Aug. 2, 1945, that an arrhythmia was first detected. On this date, and on frequent occasions during the next few months, a bigeminal rhythm was present. The dominant rhythm was slow, at a rate of from 18 to 23 per minute. The bigeminy was unusually persistent and could not be terminated by such influences as deep breathing, change of posture, exercise, oculobulbar or carotid sinus pressure, nitroglycerine, or intravenous atropine sulfate. At no time had digitalis been administered.

Laboratory study revealed the following: The blood count and the blood sugar and urea nitrogen concentrations were normal. Urinalysis was negative except for a trace of albumin. The erythrocyte sedimentation rate was 44 mm. in one hour. The blood Wassermann reaction was negative. A teleroentgenogram of the chest showed moderate left ventricular hypertrophy and dilatation, a normal vascular shadow, and clear lung fields. Frequent electrocardiograms, which will be analyzed in detail, disclosed the presence of an atrionodal rhythm with ventricular bigeminy.

The diagnosis was as follows: Hypertensive and arteriosclerotic heart disease, left ventricular hypertrophy and dilatation, coronary artery sclerosis, atrionodal and idioventricular rhythm with ventricular bigeminy, anginal syndrome. It was thought that she might also have syphilitic aortitis with coronary ostial stenosis.

The patient developed symptoms of mental deterioration and in September, 1945, was committed to the Greystone Park Sanitarium. The psychiatric diagnosis was cerebral arteriosclerosis with psychosis.

ANALYSIS OF ELECTROCARDIOGRAMS

Frequent electrocardiograms were obtained. The tracing in Fig. 1 (Aug. 23, 1945) is illustrated in order to demonstrate the usual pattern of the various complexes for this patient. Sinus bradycardia was present, with a rate of 56 per minute. The P-R interval was 0.24 second in duration. The electrical axis was deviated to the left. The QRS complexes were slurred as they rounded into elevated RS-T segments in Leads II and III. The precordial leads, CF_1 to CF_6 inclusive, were not remarkable, except for similar slurring of the QRS complexes. This tracing did not differ materially from the first one made in September, 1940, except for the slight prolongation of A-V conduction present in the last tracing.

On five occasions a bigeminal rhythm was recorded, and it is with an analysis of these tracings that we are particularly concerned. Electrocardiograms which appear in Fig. 2 were taken Aug. 2, 1945. In Lead Ia, the third and fourth beats were of normal sinus origin. The P-R interval was 0.17 second. The RS-T

segments were slightly depressed. The first, fifth, and seventh ventricular complexes of Leads Ia and the first, third, fifth, and seventh complexes of Lead Ib were of atrionodal origin. They differed only slightly in contour from the normal sinus beats, with the exception of the fifth ventricular complex in Lead Ia, which was markedly aberrant due to defective conduction in the right bundle branch. Each of the atrionodal beats was coupled with a supraventricular beat of unknown origin (second, sixth, and eighth in Lead Ia and the second, fourth, sixth, and eighth ventricular beats in Lead Ib), which differed slightly in contour from both the normal sinus and atrionodal beats. An auricular complex was present between each pair of ventricular beats. This P wave was aberrant. It was

Fig. 1.—Aug. 23, 1945.

upright but of lower voltage than normal. The P wave fell quite uniformly on the same phase of ventricular systole: on the descending limb of the preceding T wave. An exception is the first P wave in Ib, which was found on the upstroke of the T wave and was followed by an aberrant QRS response after a prolonged P-R interval. With the exception of this pair, and the second pair in Ia, the coupling was fixed; the interval between two successive complexes was 0.67 second. The interval between dominant atrionodal beats varied from 2.62 to 3.28 seconds, corresponding to rates of 23 to 18 per minute. Since this rate was

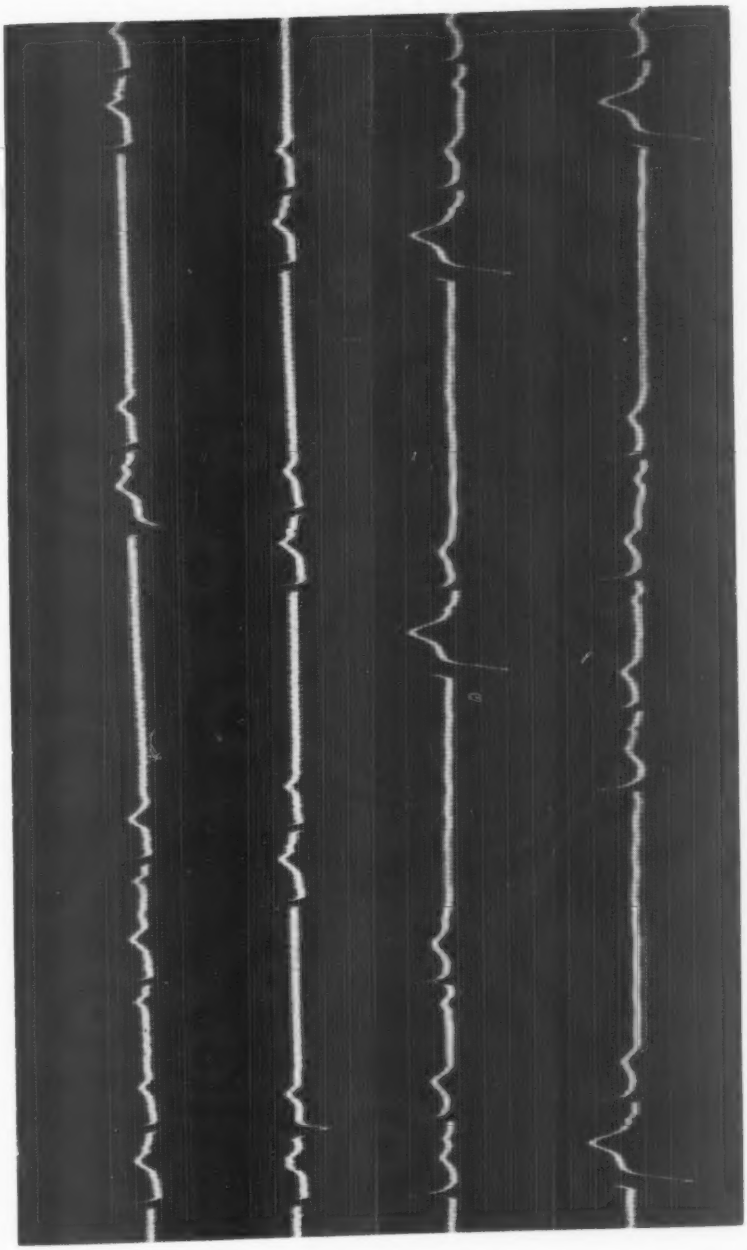

Fig. 2.—Aug. 2, 1945.

much slower than the usual rate of an A-V nodal rhythm, it is probable that either the A-V node was markedly depressed, along with other automatic centers, or that the interpolation of the coupled beat temporarily depressed the A-V nodal pacemaker. The latter explanation is more likely correct since on other occasions when two independent A-V nodal beats occurred in succession, the interval was 1.16 seconds in duration, corresponding to a rate of 51 per minute.

The third and eighth cycles of IIa and the fifth and sixth cycles of IIb were of normal sinus origin. The P-R interval varied from 0.20 to 0.24 second. A-V nodal beats appeared at the following positions: the first beat in IIa and the third in IIb. The fourth and sixth ventricular beats in IIa and the first and seventh in IIb were idioventricular in origin. Both the A-V nodal and idioventricular beats were coupled in each instance with a second ventricular beat, and a P wave appeared between the two. The P wave in this lead, also, was upright and slightly aberrant. The couplets dominated by A-V nodal beats showed an R-R interval identical with that in Lead I, while in the couplets which were introduced by idioventricular beats, the R-R interval was prolonged to from 0.76 to 0.80 second. The interval between dominant idioventricular beats was 3.44 seconds, corresponding to an inherent rate of 17 per minute.

Leads III and IV repeated the same general trend as Leads I and II and are not shown in this illustration. P_3 was inverted.

On Aug. 9, 1945, an unusually persistent bigeminal rhythm occurred (Figs. 3*A* and 3*B*). On this date ninety-seven couplets were registered, and the first seventy-one were in sequence until a single interposed sinus beat interrupted this mechanism (Fig. 3*A*, Lead III). The R-R cycle length of the dominant rhythm varied from 2.28 to 2.47 seconds, but the coupling was constant at 0.57 second. The P waves again were aberrant and also differed in contour from analogous beats in Fig. 2 and indicated a slightly different focus of origin. The second QRS complex of each couplet was abnormal in appearance and widened to 0.12 second; this aberrance indicated functional block in the right bundle branch. In Fig. 3*B* a portion of Lead II is shown. This is a continuous tracing which illustrates the fixed coupling despite variations in the interval between the second beat of the couplet and the next dominant atrionodal beat.

On three other occasions a prolonged bigeminal rhythm was recorded. The bigeminy was not interrupted by change in posture, exercise, deep breathing, or oculobulbar or carotid sinus pressure. On one occasion, while a bigeminal rhythm was in progress, 0.0013 Gm. of atropine sulfate was administered intravenously with interesting consequences (Fig. 4). In the control record, the R-R interval of the dominant nodal rhythm varied from 2.40 to 2.43 seconds. The coupling interval was 0.60 second. One minute after the injection of atropine sulfate, a triple rhythm appeared. The first ventricular beat of each triplet was of atrionodal origin, the second beat was similar to that in the control and showed aberrant conduction, while the third ventricular beat was preceded by an abnormal P wave with a short interval of 0.08 second. When triplets occurred on other occasions in Lead II, the P wave preceding the third ventricular element was also upright. Therefore, this beat may be an auricular extrasystole. The

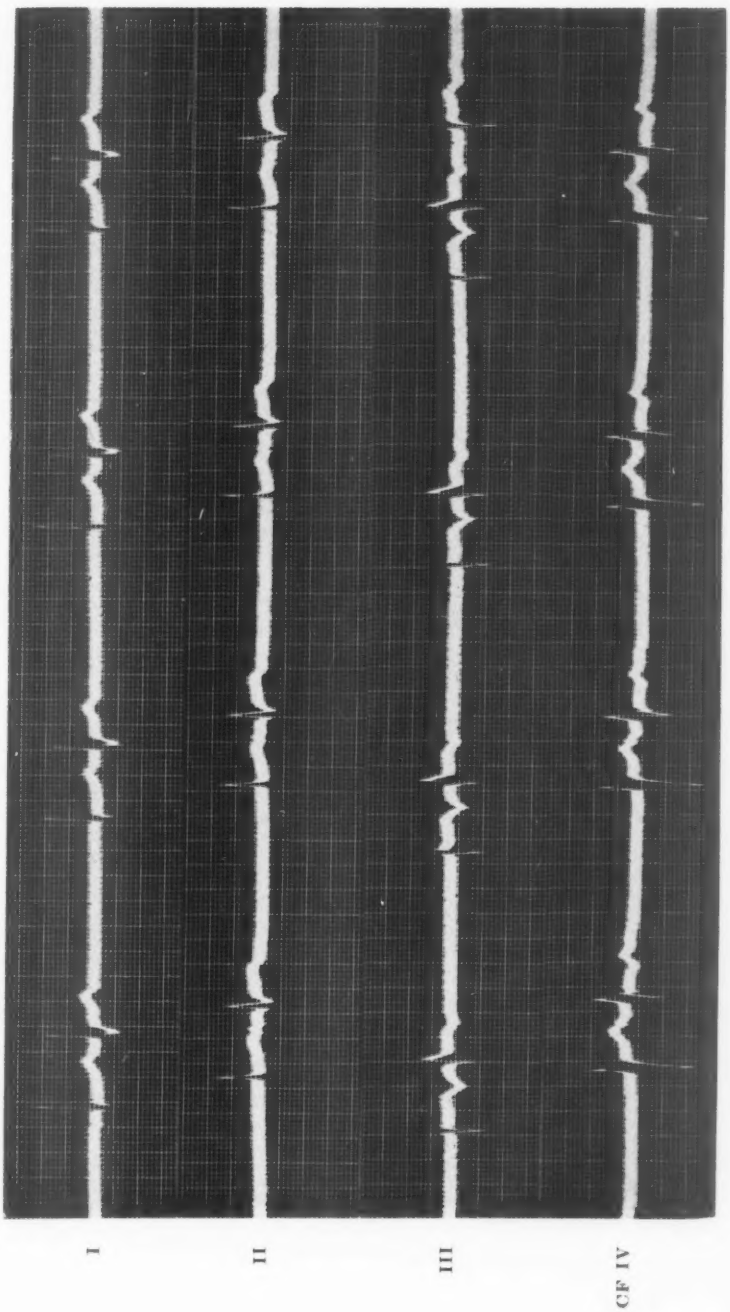

Fig. 3A.—Aug. 9, 1945.

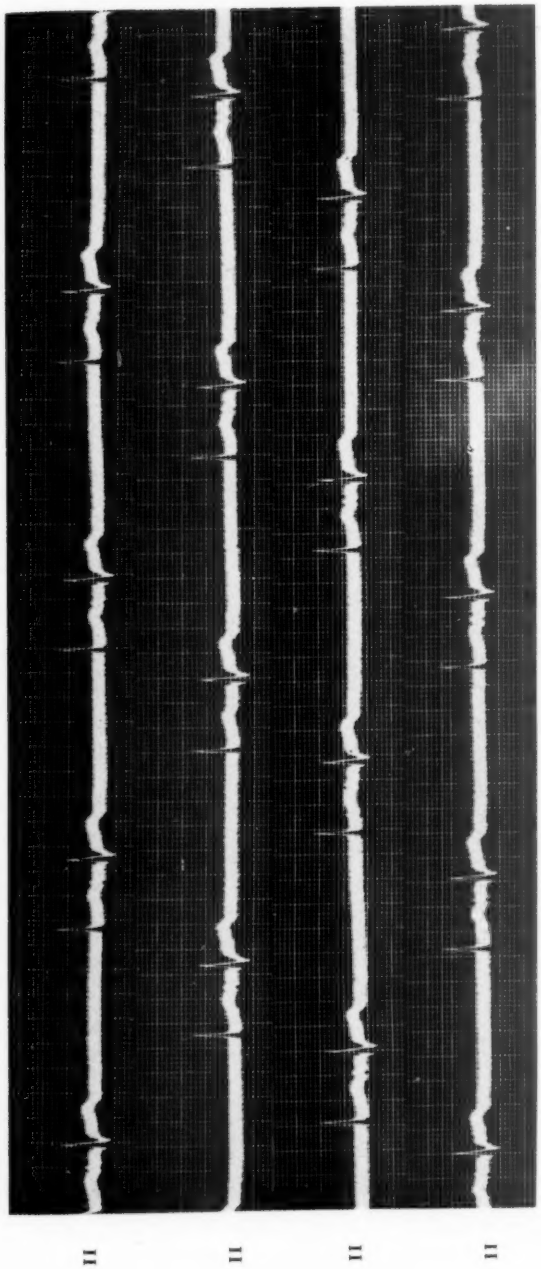

Fig. 3*B*.—Continuous tracing of portion of Lead II. R-R intervals as follows: R_1-R_2, 0.57; R_2-R_3, 1.74; R_3-R_4, 0.57; R_4-R_5, 1.70; R_5-R_6, 0.57; R_6-R_7, 1.74; R_7-R_8, 0.57; R_8-R_9, 1.71; R_9-R_{10}, 0.57; R_{10}-R_{11}, 1.75; R_{11}-R_{12}, 0.57; R_{12}-R_{13}, 1.75; R_{13}-R_{14}, 0.57; R_{14}-R_{15}, 1.80; R_{15}-R_6, 0.57; R_{16}-R_{17}, 1.78; R_{17}-R_{18}, 0.57; R_{18}-R_{19}, 1.73; R_{19}-R_{20}, 0.57; R_{20}-R_{21}, 1.77; R_{21}-R_{22}, 0.57; R_{22}-R_{23}, 1.72; R_{23}-R_{24}, 0.57; R_{24}-R_{25}, 1.72; R_{25}-R_{26}, 0.57; R_{26}-R_{27}, 1.71; R_{27}-R_{28}, 0.57; R_{28}-R_{29}, 1.66; R_{29}-R_{30}, 0.57; R_{30}-R_{31}, 1.74; R_{31}-R_{32}, 0.57; R_{32}-R_{33}, 1.76; R_{33}-R_{34}, 0.57; R_{34}-R_{35}, 1.72; R_{35}-R_{36}, 0.57.

R-R interval between the first and second beats was fixed at 0.53 second; the interval between the second and third beats varied from 0.52 to 0.62 second. The interval between the dominant A-V beats was 2.00 to 2.04 seconds. Three minutes later the rhythm was again bigeminal in character. The rate of the dominant rhythm had become accelerated, and the R-R interval was 1.50 seconds, while the coupling time had decreased to 0.50 second. Five minutes later, the

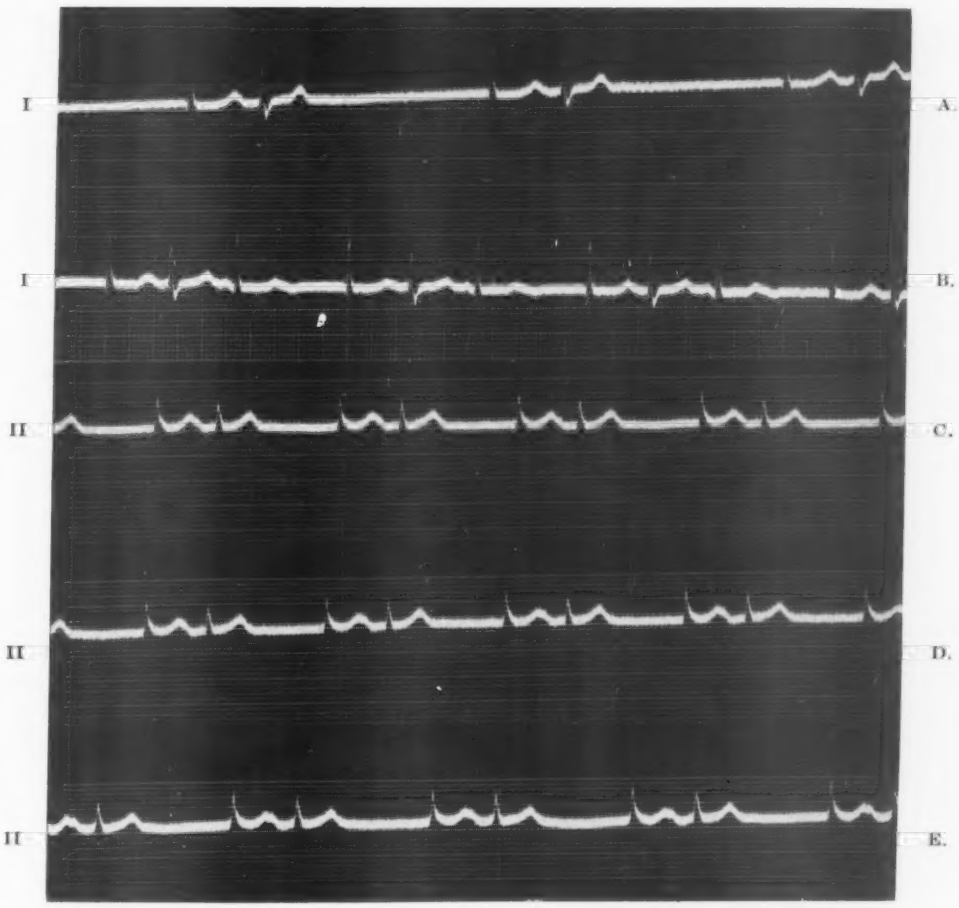

Fig. 4.—Aug. 27, 1945. *A*, Control record. *B*, One minute after intravenous atropine sulfate. *C*, Three minutes later. *D*, Five minutes later. *E*, Thirty minutes later.

dominant A-V rhythm presented a cycle length of 1.48 second and the coupling interval was still 0.50 second. At the end of thirty minutes the dominant rhythm had slowed, with a cycle length of 1.64 seconds, and the couplet interval had increased to 0.52 second.

In Fig. 5 are shown A-V nodal beats which were preceded in Lead II by inverted P waves. We interpret this to show that retrograde conduction could

occur normally under certain circumstances. The A-V nodal beats which were preceded by retrograde P waves invariably occurred at an interval after the preceding beat which was shorter than the usual interval between nodal beats in this case. This suggests that facilitation of retrograde conduction took place when one nodal beat followed another at a comparatively short interval.

A triple rhythm was seen under the following circumstances: after stimulation of the right carotid sinus, after the administration of atropine sulfate, and also on one occasion as a spontaneous phenomenon.

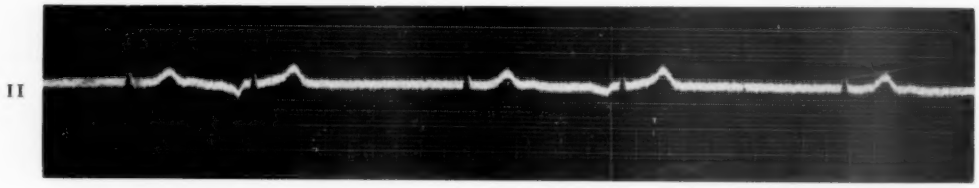

Fig. 5.—Aug. 21, 1945.

Comment.—Analysis of the electrocardiograms yielded the following pertinent data:

1. An unusual and remarkably persistent type of atrionodal rhythm with ventricular bigeminy was present. In all, 270 couplets were recorded, and the longest consecutive run consisted of seventy-one pairs.
2. Between the bigeminal ventricular beats an antegrade but aberrant auricular complex was present.
3. Rarely the first beat of the couplet was an idioventricular escape beat.
4. On some occasions, the second ventricular beat was aberrant, due to functional right bundle branch block.
5. The coupling was consistently fixed on any given day, although it varied slightly from day to day. The interval varied from 0.57 to 0.72 second when the dominant rhythm was atrionodal in origin, and from 0.76 to 0.80 second when idioventricular beats were dominant.
6. Despite slight, or even marked variations in the interval between dominant atrionodal beats, the coupling of the second beat to the first remained fixed.
7. Two exceptions to this rule occurred in Fig. 2, in which one couplet was shorter and one longer than the other pairs present on this occasion.
8. The rate of the dominant rhythm was unusually slow at times and was as low as 18 per minute.
9. The bigeminy was not influenced by change of posture, exercise, respirations, oculobulbar or carotid sinus pressure, or nitroglycerine.
10. After administration of atropine sulfate intravenously, the rate of the dominant rhythm was accelerated. However, the pairing was not interrupted, although the cycle length of the bigeminy was shortened.
11. A triple rhythm occurred spontaneously, after pressure on the carotid sinus, or one minute after the intravenous administration of atropine. The

last beat of each triplet was probably of abnormal auricular origin and was not coupled to the preceding beat at a fixed interval.

12. The bigeminy never occurred without the presence of the intervening abnormal auricular beat and the latter never appeared independently, or without being followed by a ventricular response.

DISCUSSION

We could discover in the literature only three cases of atrionodal rhythm with ventricular bigeminy and an intervening antegrade P wave. Gallavardin, Dufourt, and Petzetakis[12] reported the first one in 1914. They believed two independent rhythms, one atrionodal, the other sinoauricular, were present. This was clearly an instance of interference dissociation. White[14] described a case of reciprocal rhythm in 1921 in which on one occasion the P wave between ventricular beats was upright. As an explanation of this phenomenon, he suggested that the mechanical theory might apply to reciprocal rhythm, that the abnormal auricular beats were excited by the contractions of the ventricles and were in turn followed by ventricular responses. Herve and Besoain (1942)[10] described a case in which, preceding the onset of the bigeminal rhythm, the pacemaker in the sinus node shifted to a lower center. A pause then ensued and the atrioventricular node escaped. This escape beat was followed in turn by a supraventricular beat in which the P wave was identical with the last one before the pause and, therefore, originated in an abnormal location in the sinoauricular node. A run of bigeminy, consisting of paired nodal escape and abnormal sinoauricular beats, then occurred. The authors did not attempt to explain the mechanism of this arrhythmia. The tracings in their publication were so reduced in size that accurate measurement was impossible, and we do not know whether or not the coupling was fixed.

Our case resembled superficially those described in the foregoing. However, the mode of onset and termination of the bigeminy differed from the transitions which occur in interference dissociation, and we were unable to demonstrate a shifting pacemaker prior to the onset of the bigeminy. The bigeminy was more persistent than in any previously reported cases and allowed more detailed observations to be made.

The first explanation of the mechanism which suggests itself is that the bigeminy may be due to the fortuitous pairing of two independent rhythms. To rule out this possibility the following facts are offered:

1. The rhythm was unusually persistent. It is conceded that in some instances of A-V interference dissociation there may be short intervals during which the rates of the two rhythms are identical, or nearly so. However, the sinus rhythm sooner or later is accelerated, and when it exceeds the rate of the A-V node, it resumes command of the entire heart. The bigeminy in our case did not terminate in this manner.

2. The abnormal P wave never appeared independently but always followed a preceding atrionodal beat. If the two rhythms were unrelated, we would expect the second to precede the first at some time.

3. The coupling was fixed for long periods of time despite slight to marked variations in rate of the dominant rhythm. On one occasion the fixed coupling was maintained throughout a sequence of seventy-one pairs of beats.

4. The coupling was not interrupted by exercise, change of posture, forced breathing, oculobulbar or carotid sinus pressure, nitroglycerine, or intravenous atropine sulfate. If there were two independent rhythms present, it is reasonable to anticipate that they would react in different degree to the foregoing stimuli.

5. The rate was too slow both for an independent A-V rhythm and a nomotopic or ectopic auricular rhythm.[15]

It is, therefore, probably safe to conclude that the coincidence of the two rhythms was not fortuitous but that the second one was linked in some way with the first. It may further be assumed that the abnormal auricular beat was excited by the preceding ventricular contraction and was, in turn, followed by a ventricular response. Determination of the origin and mechanism of the P wave in question holds the key to the solution of this case. Study of the P waves reveals the following: They were abnormal for this case. They were obscured to some extent by the fact that they fell on the descending limb of the preceding T wave, but they could be seen to differ definitely in contour from obviously normal S-A complexes. The P waves presented an antegrade pattern. They were upright in Leads I and II and inverted in Lead III. How then can the dependence of an abnormal antegrade P wave on a preceding ventricular beat be explained?

Two possibilities are presented for consideration. Either the two beats are connected electrically or the coupling is due to some other mechanism.

If there is electrical continuity between the first ventricular beat and the P wave which follows, can this case be one of reciprocal rhythm? And if it is reciprocal rhythm, how can the absence of a retrograde P-wave pattern be explained? As a corollary to the last question, it may be asked, can a stimulus which originates in the A-V node, and secondarily excites the auricle, cause an antegrade P-wave pattern? From the electrical standpoint this would appear impossible, certainly if there were present a normal pathway for retrograde conduction. However, from time to time the statement appears in the literature that an A-V nodal beat might give rise to an upright P wave in Lead II. Gallavardin and Gravier[16] proposed that variations in the form and position of the P wave depend upon the portion of the auricle upon which the impulse from the A-V node impinges first. They pointed out that the stimulus from the A-V node need not fall first upon the lower part of the auricle but that it may reach its upper portion first because of distribution of conducting tissue in the auricles. Chamberlain[17] endorsed this concept. McQuire and Rosenberger[18] and Edens[19] also agreed that nodal P waves need not be inverted. Lewis[20] stated that the P wave in A-V nodal rhythm is inconstant in form but usually inverted. Experimentally, Scherf and Shookhoff[21,22] and Rothberger and Scherf[23] showed that the P waves in nodal rhythm may be upright but abnormal in form. Katz[24] designated as coronary nodal rhythm those cases in which upright P waves precede QRS responses by a short interval and suggested that the P waves originated

in the upper strands of the A-V node which lie in the auricle near the sinus node. Langendorf, Simon, and Katz[25] suggested that there may be present intra-auricular block which makes the path resemble that taken by sinus beats.

Although there may be some reasonable difference of opinion on this point, the majority of present-day investigators agree that an A-V nodal impulse cannot give rise to an antegrade P wave. Moreover, in the case which we have presented there is evidence that retrograde conduction could take place, for occasionally an inverted P_2 did precede a ventricular response. If reciprocal rhythm were present, we might expect to find an inverted P_2 between the ventricular contractions.

Consideration must be given next to the possibility that although this case is not one of reciprocal rhythm, nevertheless there is electrical continuity between the two beats; that is, the auricular beats may be extrasystoles coupled with a dominant A-V nodal rhythm. Since the coupling was fixed, it might be argued that the extrasystoles were due to re-entry. However, in order to have re-entry, it is first necessary to demonstrate entry. There is a remote possibility that retrograde conduction to the auricle did accompany the first ventricular beat but that the auricular component in the electrocardiogram was buried in the QRS complex. The next auricular beat might then be coupled as a re-entrant phenomenon with this retrograde auricular impulse. However, the evidence in our case tends to negate this hypothesis. Coupling occurred after idioventricular beats as well as after atrionodal beats. Retrograde conduction following ventricular beats is, in itself, a rarity. Usually the R-P interval is somewhat longer than that following A-V nodal beats and the P wave can be seen superimposed on the S-T segment or T wave. We found no evidence of retrograde conduction with idioventricular beats in our case. This theory would not explain the response to intravenous atropine, in which the coupling interval was decreased. This response would necessitate the assumption that the re-entrant pathway had become shortened following diminished vagal tonicity. Furthermore, exercise, which might be expected to cause disappearance of extrasystoles, was without influence upon the bigeminy.

Since we cannot demonstrate electrical connection between the two beats, we must turn to consideration of another mechanism by means of which one beat might provoke another, the so-called mechanical theory. This theory was first invoked by Cohn and Fraser[26] to explain premature auricular contractions which occurred at a short interval after ventricular systole in complete heart block. Wilson and Robinson[27] suggested that the same effect of ventricular systole upon the normal sinus pacemaker might account for the peculiar sinus arrhythmia encountered in complete heart block. Barker[28] demonstrated in animal experiments that a sudden increase in intraventricular pressure would initiate a premature ectopic auricular beat. He assumed that the ventricular contraction mechanically stimulated a focus in the bundle above the supposed lesion and provoked a premature beat which was conducted through the auricles by the normal path. White[14] offered the mechanical theory as an alternate explanation for one of his cases of reciprocal rhythm. Wolferth and McMillan,[29]

however, objected to this theory and pointed out that the R-P′ interval in reported cases was too short to accommodate Barker's double mechanism. They presented an analysis of three cases of ventriculoauricular sequential beats with relatively short R-P′ intervals and concluded that this arrhythmia was best explained on the basis of retrograde conduction. Moreover, they were unable to prove mechanical stimulation of the auricle by ventricular systole in animal experiments. Later observers have been unanimous in rejecting the theory of mechanical stimulation (Winternitz and Langendorf,[30] Parkinson,[31] Parsonnet and Miller,[32] Scherf,[33] and Kisch and Zucker[34]). Thus, although cardiac muscle tissue, in common with other types of muscle tissue, does respond to direct mechanical stimulation, there is no experimental or electrocardiographic evidence that contraction of the ventricle in itself constitutes a proper stimulus to cause an auricular systole.

None of the foregoing theories is adequate to explain the mechanism in our case, nor can we offer a more plausible one. Any acceptable theory must account for the unusual persistence of the bigeminy, the lack of response to the sinus reactions, the coupling with idioventricular beats, the response to atropine, the rare exceptions to the rule of fixed coupling, the presence of triplets, and the unusually slow dominant rhythm. We are led to the conclusion that this is another example of the fact that one beat may in some unknown way stimulate a second one. If the trigger mechanism by which this stimulation occurs were known, many perplexing problems in electrocardiography might be clarified.

SUMMARY

1. A case of atrionodal rhythm with ventricular bigeminy of unusual mechanism is presented.

2. The sequence of events was probably as follows: Periodically there occurred marked depression of the sinus nodal pacemaker accompanied by depression of the lower automatic centers as well. As a result, sinus pauses occurred, with either the A-V node or the ventricle taking command of the heart, either as a series of escape beats or as a dominant atrionodal or idioventricular rhythm. The dominant beats were followed at a fixed interval by abnormal auricular complexes which originated either in the S-A node, outside of the normal pacemaker, or in the auricle. The auricular beats were followed in turn by ventricular responses which were normal or aberrant in contour. Apparently the second ventricular systole led to further depression of the dominant pacemaker so that the rate was unusually slow.

3. The possible mechanisms which might account for this unusual bigeminy were reviewed but none was found applicable to this case.

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A NEW SENSITIVE PORTABLE PLETHYSMOGRAPH

G. E. Burch, M.D.
New Orleans, La.

FOR several years studies have been conducted on peripheral blood vessels at Tulane Medical School and the Rockefeller Institute for Medical Research with the use of a sensitive plethysmograph. The apparatus went through various stages of development from time to time as each new unit was constructed. In most instances the units were not portable and in many ways rather difficult to use. It was not possible, for example, to obtain linear variations in the plethysmogram in standard units without a process of fairly lengthy calculations to correct for size of the part and sensitivity of the recorder. The sensitive recording capsules were made of a thin rubber membrane which disintegrated very rapidly, resulted in difficulties with leaks, and necessitated constant service. Because of these and many other difficulties it was decided to build a sturdy, portable, and practical plethysmograph for clinical and experimental purposes which would require no constant servicing and which would record a plethysmogram that could be standardized and read easily and directly just as one reads an electrocardiogram. It, therefore, is the purpose of this paper to describe the model of a sensitive portable plethysmograph developed in our laboratory, to indicate in detail the use of the one now available,* and to point out some of the fundamental aspects of recording, interpreting, and applying the plethysmogram to physiologic and clinical problems. It is not the purpose of this discussion to review the development of plethysmography nor to review the physiologic or clinical applications of plethysmography in detail.

THE PLETHYSMOGRAPH

The model of the plethysmograph constructed in our laboratory is shown in Figs. 1 to 4. It consists of (1) a sensitive volume-recording metal bellows or capsule which activates a mounted bow and bowstring, (2) lighting and lens systems for focusing the bowstring, (3) a coarse volume recording sytem, (4) timers, (5) a camera, and (6) a selector valve. These parts are shown in Figs. 1 to 4.

The principle and mechanics of the apparatus are very simple. A diagrammatic representation of the apparatus is shown in Fig. 1. The pneumatic system

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*The plethysmograph that will be described is now made by the Cambridge Instrument Company of New York, New York, N. Y.

consists of the sensitive metal capsule (*d'*, Fig. 1, *B*, and Fig. 3), a metal bellows (*p*, Fig. 1, *C*, and Fig. 4) to control the position of the bowstring, and an extremity cup (Fig. 5, *C*). These three units are connected together at atmospheric pressure by means of a thick-walled and narrow bore (1 mm.) rubber tubing. Once the pneumatic system is closed, any change in volume of the part enclosed in the extremity cup produces a change in volume of the sensitive metal capsule (*d'*, Fig. 1, *B*, and Fig. 3). When this sensitive metal capsule moves, it activates

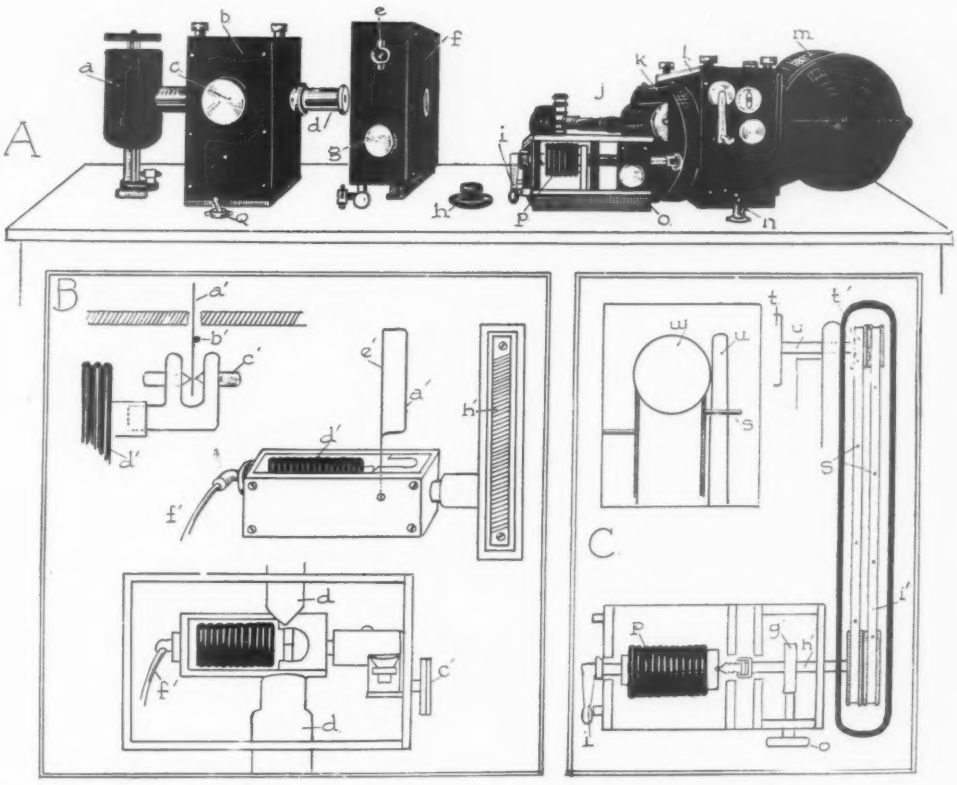


Fig. 1.—Diagram of the plethysmograph developed in our laboratory. The details are described in the text. This plethysmograph served as the model for the instrument that is now available commercially (Fig. 6).

a very short arm of a light aluminium tube (weight, less than 30 mg.), shaped essentially as a question mark (?), about a pin or axis set preferably in jewel bearings. The relatively very long or bow-shaped end (*a'*, Fig. 1, *B*) moves a great deal (mechanical magnification, 40×). On this bowstring is stretched a fine tungsten string (*e'*, Fig. 1, *B*) which is enlarged about 150 times and focused by satisfactory lenses (*d*) onto the moving photographic paper of an ordinary type electrocardiograph camera. Satisfactory arrangements are made so that photographing can be done in a room with ordinary amounts of lighting. The

selector valve (*h*, Fig. 1, *A*) is connected to three rubber tubes which in turn may be connected alternately to three extremity cups or parts. Also connected to the pneumatic system is another bellows, a coarse recorder bellows or baseline adjustment bellows (*p*, Fig. 1, *A*). The volume within this bellows can be varied by turning the knob, (*o*, Fig. 1, *A*). When this knob is turned, the shaft, to

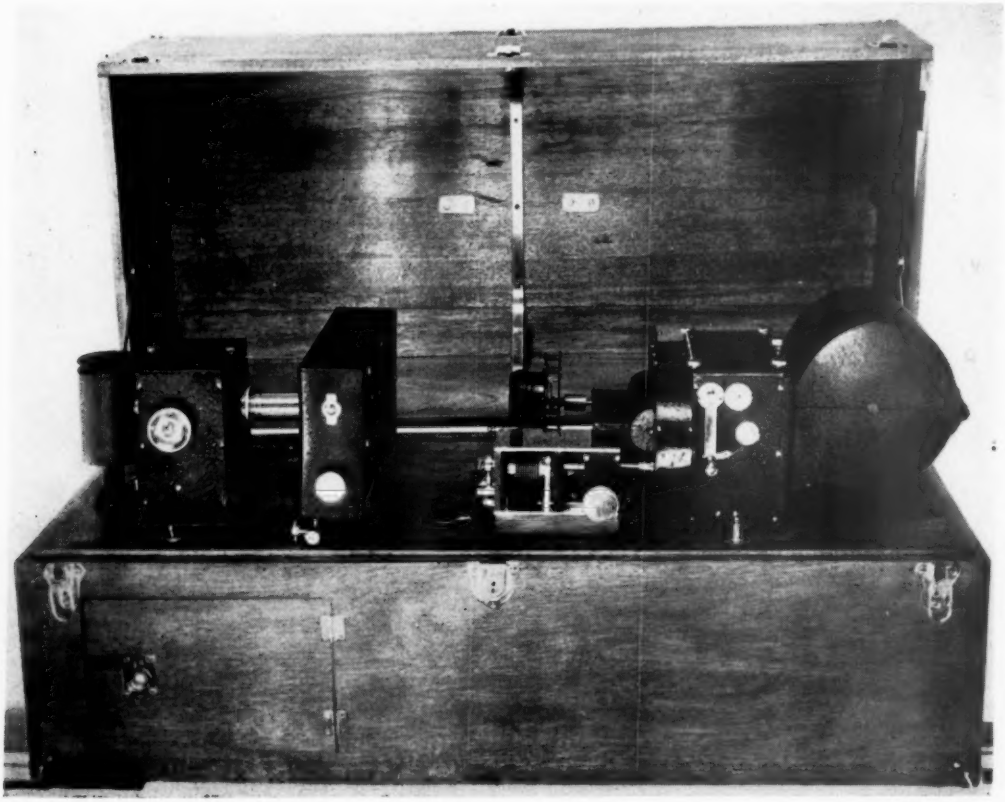


Fig. 2.—Photograph of the plethysmograph constructed and used in the laboratory. From left to right are seen (1) the lamp, (2) the housing and lens system for the sensitive recording bellows, bow, and bowstring, (3) the timer housing and lever for making the necessary changes for slow and speed recording, (4) the selector valve, (5) the calibrator level, (6) the baseline recorder, (7) the interval elapsed timer recording pins and baseline recorder pins, and (9) the camera. The exposed photographic paper receiver is located under the camera.

which are attached a screw on one end and a pulley on the end near the camera, is rotated. Any change in volume of the baseline adjustment bellows produces a shift in the sensitive metal capsule, thus moving the bow and bowstring. At the same time the pulley attached to the other end of the shaft rotates and moves a metal tape (*i'* Fig. 1, *C*) on which are attached metal pins (*s*, Fig. 1, *C*) which cast shadows on the photographic paper. The pins are so spaced that one

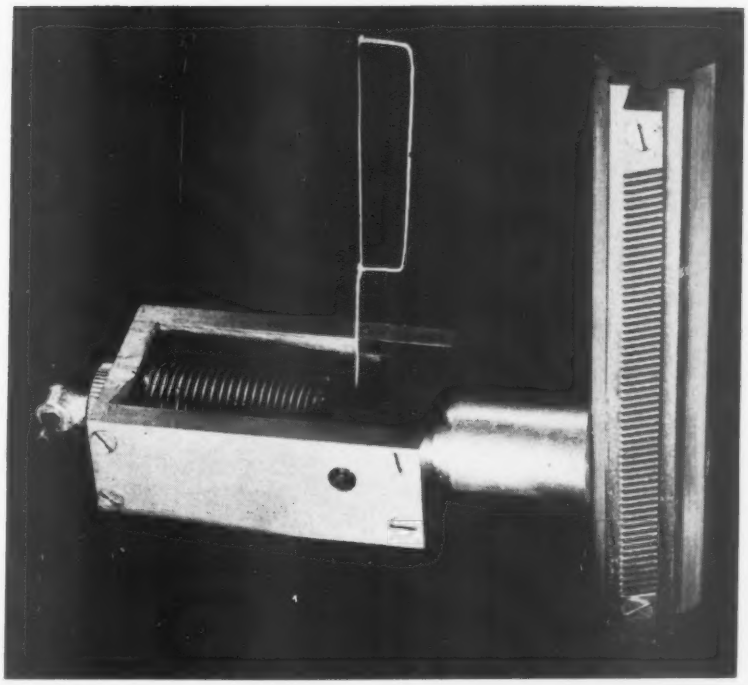


Fig. 3.—Photograph of the sensitive bellows, bow, and bowstring assembly mounted on a rack. The bowstring rotates around the watch type of steel bearing. The bellows was changed later to a dome-shaped aluminum membrane which activates the bow and bowstring in a similar fashion.

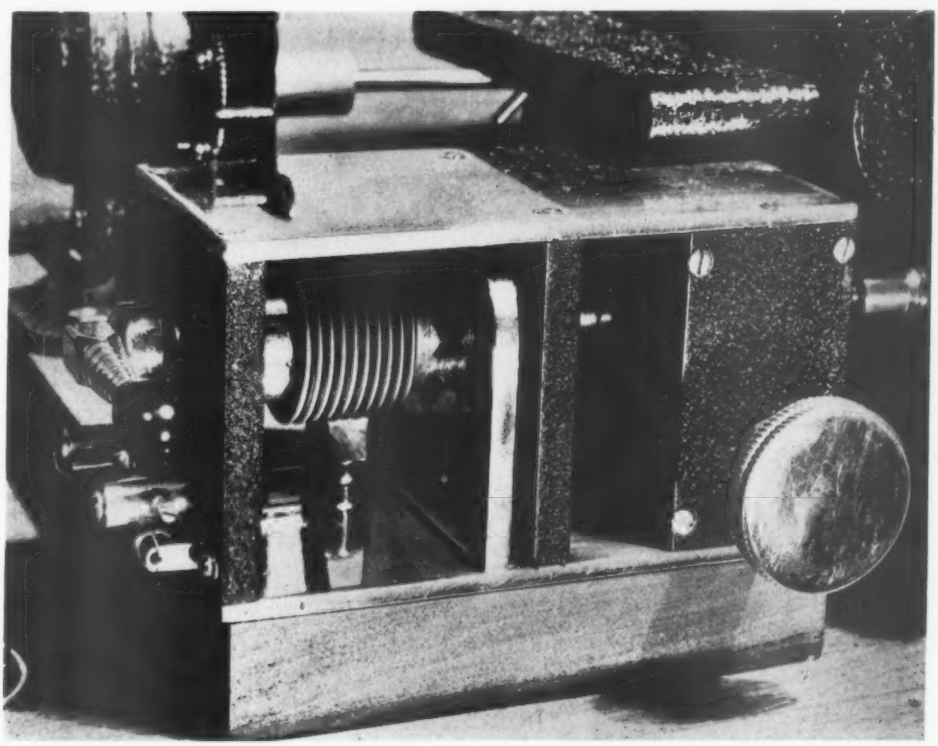


Fig. 4.—A photograph of the calibrator lever, baseline adjustment bellows, and knob which controls a worm and gear. Consult the text and Fig. 7 for the details.

is always casting a shadow on the photographic paper. A movement of the pin shadows of 1.0 mm. represents 1 c.mm. volume change in the pneumatic system.

On the other end of the housing of the baseline adjustment bellows is another screw fixed to a calibration lever (*i*, Fig. 1, *C*). By means of stops adjusted by set screws, a partial rotation of the *calibration lever* (*i*, Fig. 1, *C*) effects a 10 c.mm. change in volume within the pneumatic system. This change in volume results in a movement of the bowstring, thus making it possible to convert linear change

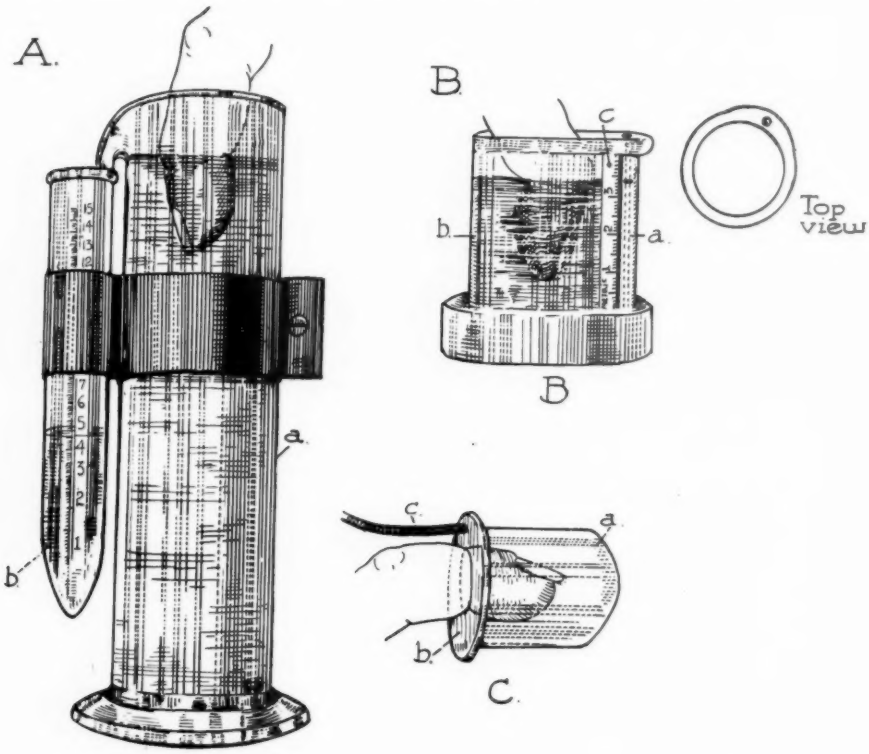


Fig. 5.—Drawing of the apparatus, *A* and *B*, used to measure the volume of that part for study. In *A*, the volume of water displaced by the part spills from the cylinder, *a*, to the graduated test tube, *b*, for measurement. In *B*, the volume of water displaced by the part displaces a meniscus in the narrow bore tube, *a*, which connects with cylinder, *b*, near the base. Consult the text for details and other methods. *C* shows an extremity cup in place.

in the bowstring shadow of the completed plethysmogram to cubic millimeter change in volume of the part enclosed by the extremity cup. Since the parts of the extremity (finger and toe tips) vary in size, it is necessary to adjust the sensitivity of the bowstring in order to reduce all linear movements of the string shadow to a standard unit of volume of a standard-sized part. The sensitivity of the bowstring is varied by means of the sensitivity adjustment knob (*c*, Fig. 1, *A*) which rotates a pinion and lifts or lowers the sensitive metal capsule, bow, and bowstring which are mounted on a rack. This makes it possible to focus

a small segment of the bowstring near the fulcrum of the bow or a segment farther away. Thus, by varying the length of the lever, it is possible to select, within desired limits, a relatively large or relatively small amount of movement of the string shadow for a given change in volume within the pneumatic system (see paragraph on Standardization of the String).

During the course of recording, it is sometimes advisable to discontinue the actual recording in order to save photographic paper and to avoid the accumulation of a cumbersome record; at the same time, the interval of time that elapses when the camera is off is often important to know and record. This is done automatically by a *master timer* or *elapsed time indicator*, synchronous timer (*t*, Fig. 1, *C*) which rotates a pulley and metal tape (*t'*, Fig. 1, *C*). Fixed to the tape are four pins of different diameters which cast shadows of different widths on the completed plethysmogram. A movement of a timer pin shadow of 4 mm. is equivalent to the elapse of one minute in time. From the width of the timer pin shadows and their relative positions before stopping the recording and at the beginning of the next interval of recording, the duration in time that the camera was off is measurable to a fraction of a minute. This feature is of value when the effects of stimuli, drugs, and other agents are being studied.

The plethysmograph made available commercially is shown in Figs. 6 and 7. The detail descriptions of the unit are indicated in the legends. All future references and discussions will be concerned with this unit.

Horizontal millimeter lines and time lines are produced on the plethysmogram in a manner similar to that in the electrocardiograph. One timer produces a vertical mark every 0.04 second in the same fashion used in electrocardiography and the other, a shadow every 15 seconds. By means of a speed control knob or lever (Figs. 1 and 6, *22*) a simple rotation of the lever results in a change in the speed of the camera with a movement of the recording paper from a rate of 9.5 cm. a minute (slow speed) to about 145 cm. per minute (fast speed) and vice versa. By means of suitable levers and switches the light intensity, the timers, and the camera speed are changed with each simple rotation of the *speed control lever* (Fig. 6, *22*). This ensures a good recording at the two speeds.

The extremity cup (Fig. 5, *C*) is made of thin-walled transparent plastic test tubes. One end is closed with a diaphragm made of the same material. The diaphragm has a hole shaped to fit the finger or toe tip loosely. Entering the cup through the diaphragm is a thin-walled brass tube to which is connected the rubber tubing from the plethysmograph. A fairly large assortment of cups should be available in order to make possible a fit for a finger or toe of any size. The cups are chosen to ensure a minimum dead space without the part resting against the wall. The finger or toe tips are inserted into the hole of the diaphragm until the edges of the hole reach the distal major dorsal and ventral skin creases at the distal interphalangeal articulation. A seal between the cup and the part is made with warm printers' roller compound brought to the proper consistency and stickiness with LePage's glue.

Physical Characteristics of the Sensitive Metal Capsule.—The crucial portion of the instrument from the physical point of view is the sensitive metal capsule

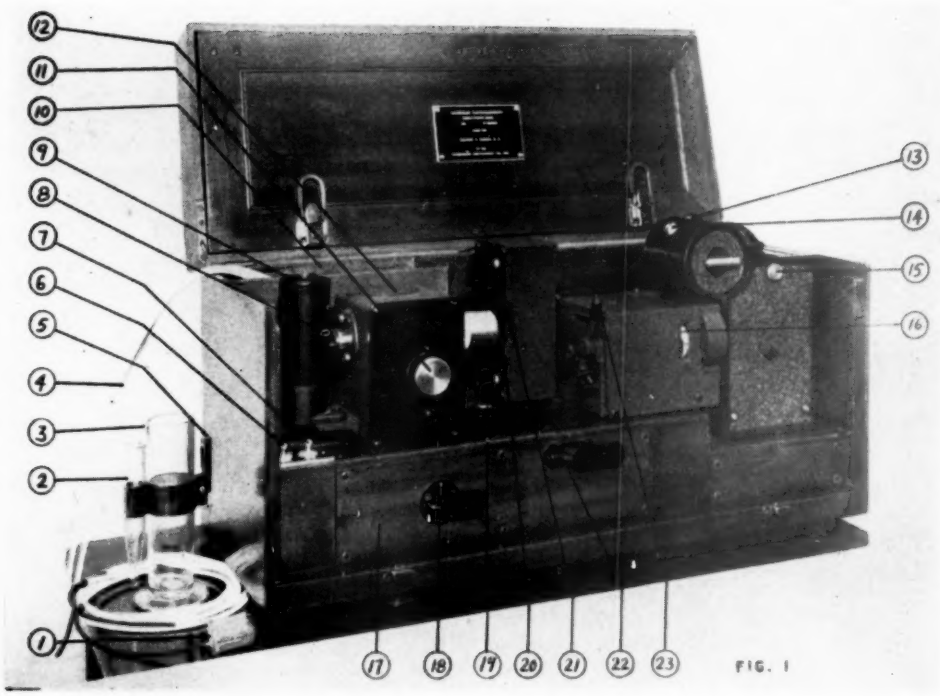


Fig. 6.—The plethysmograph commercially available. The labelled parts are *1*, extremity cup; *2*, calibrated test tube; *3*, measuring cylinder; *4*, rubber tubing leading from extremity cup to the plethysmograph; *5*, socket for power supply; *6*, light and slow timer switch; *7*, camera and fast timer switch; *8*, condenser lens; *9*, lamp; *10*, storage compartment; *11*, sensitivity adjustment knob; *12*, inspection plate; *13*, exposed photographic paper receiver; *14*, lever for opening and closing receiver and cutting the photographic paper; *15*, latch for loading the camera; *16*, knob for controlling baseline adjustment; *17*, inspection panel; *18*, selector valve; *19*, focusing screw; *20*, fast timer; *21*, slow timer; *22*, speed control lever; and *23*, calibrator lever.

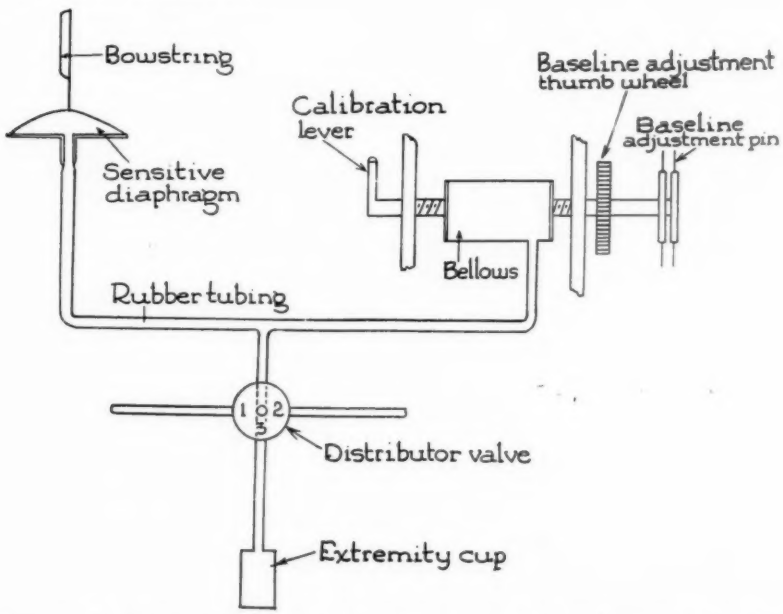


Fig. 7.—Diagram of the pneumatic system and recording parts of the plethysmograph shown in Fig. 6. Consult the text for details.

or diaphragm (0.002 inch thick aluminum) which is designed to give a true record of relatively rapid changes in volume. As pointed out by Wiggers,[1] in his discussion of the recording of pressure pulses, the vibrating membrane must have certain characteristics in order for it to reproduce accurate records of the physical phenomena to be measured.

Natural Frequency.—The natural frequency of the sensitive metal capsule is about 150 cycles per second. This more than meets the necessary requirements and also makes the instrument quite suitable for the study of animals with very rapid pulse rates, such as is encountered in the rat or in the upstroke of the pulse waves, or the dicrotic notch.

Damping.—Fig. 8 shows the string shadow of the sensitive metal capsule to be damped properly, thus avoiding errors due to overshooting or overdamping.

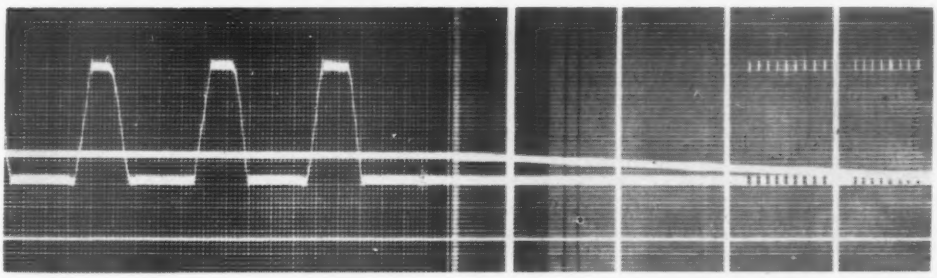


Fig. 8.—Tracing showing the adequate damping of the bowstring. A shift of the bowstring shadow represents 10 c.mm. change in volume within the system. The first portion was recorded at fast speed (standard camera speed employed in electrocardiography) and the second portion was recorded at slow speed. The time interval represented by the distance between each broad vertical white line in the slow speed recording is fifteen seconds.

Relation of Rate of Vibrations to Linear Deflection of the Bowstring.—A mechanical device in which alternate compression and release of a metal bellows produced a constant change in volume at desired rates, from very low frequencies to very high frequencies, was connected to the pneumatic system of the plethysmograph. Fig. 9 shows the results of these studies. The string shadow recorded the true volume change at complete cycle frequencies as high as are encountered in the study of human and other animal subjects. This (Fig. 9) indicates the suitability of the apparatus for the study of animals with very high cardiac or pulse rates after suitable correction.

Influence of Pressure in the Pneumatic System.—The relationship of volume change within the pneumatic system to deflection of the string shadow within the range of the working pressure (2 to 24 mm. of water) is shown in Fig. 10. Since this is a volume recorder, the fact that the linear movement of the string shadow does not vary for a given volume change within the pneumatic system within the variations in pressure used during recordings indicates an excellent physical feature of the sensitive aluminum capsule.

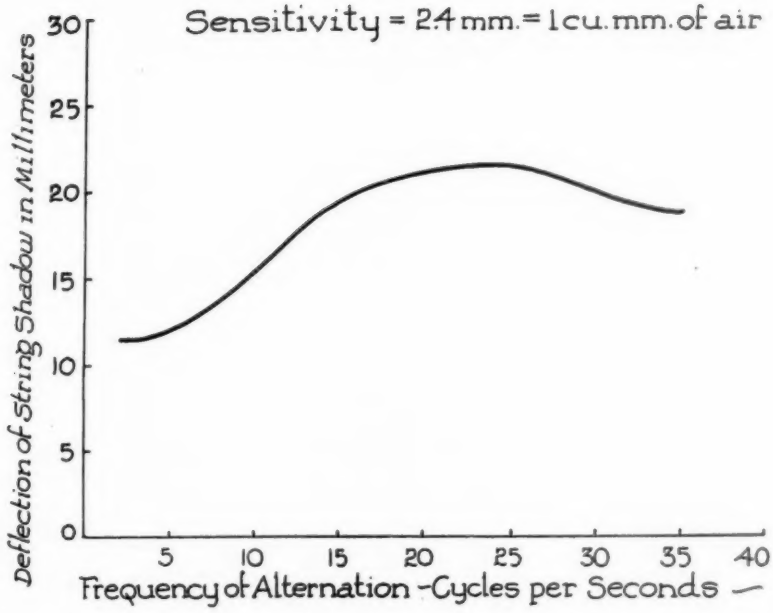


Fig. 9.—Frequency response curve of an aluminum diaphragm activated by air from a bellows being alternately compressed and released. Curve shows the variations in sensitivity of the bowstring of the plethysmograph with variations in rate of its movement. The upstroke of the pulse wave at resting heart rates has a frequency about five cycles per second.

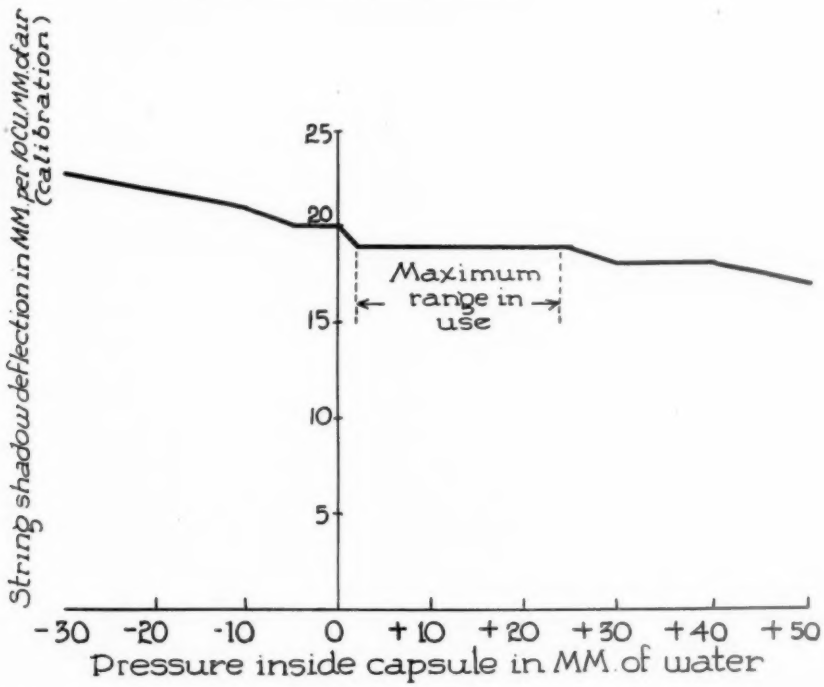


Fig. 10.—Response of .002 inch aluminum diaphragm to a standard 10 c.mm. calibration, with changing internal pressure. Variations in sensitivity of the bowstring with variations in the pressure within the closed pneumatic system. Within the pressure range of use the sensitivity of the bowstring does not vary.

METHOD OF RECORDING THE PLETHYSMOGRAM

The conditions and method for recording the plethysmogram described are intended for relatively ideal conditions of study. It is obvious that such conditions are not always available. Good work can be performed under less satisfactory conditions, but it is necessary that the standards for the normal and the method be established for the working conditions. Any comparisons with the results of others must be interpreted in the light of the circumstances of study. Once an observer becomes acquainted with his conditions of study, he will have no difficulty in applying plethysmographic methods to his patients.

The Observation Room.—When studying patients for physiologic phenomena concerned with the peripheral blood vessels of the tips of the fingers and toes, it is best to have a proper type of observation room.[2] The atmosphere of the room should be comfortable. It has been found that a temperature of about 23.8°C. (75°F.) and a relative humidity of about 50 to 60 per cent are good atmospheric conditions for a resting subject. It is also advantageous to have an air-conditioning unit which can make possible a dry or wet cold atmosphere and a dry or wet warm or hot atmosphere. This makes it possible to study the ability of the circulation to react to stimuli that produce vasoconstriction and vasodilation, reactions of great value in differentiating organic and functional occlusive vascular diseases. The room should be free of drafts of air; that is, the rate of movement of the room air should be less than fifteen feet per minute. The room should be made cozy, comfortable, and free from any intricate apparatus. This leads to relaxation on the part of the patient and reduces anxiety and other psychic phenomena to a low level. The patient should rest on a comfortable bed with the part that is to be studied held at heart level.

Clothing.—The patient should remove all clothing or at least everything except loose-fitting underwear. Covering with a sheet or blanket may be permitted. It is necessary to be careful not to allow him to become cool or warm; he must be comfortable. A patient who enters an air-conditioned room at 75°F. may want to cover because of chilliness, but he is likely to warm up and become too warm if great care is not observed. The best rule to follow is to have the patient comfortable.

Position of the Part for Study.—The part for study should rest at the level of the heart. To ensure a proper position for the finger tips, an adjustable and comfortable armrest is preferable (Fig. 11). Pillows may be used if a special armrest is not available. It is *imperative* that the extremity cup does not touch anything. It is necessary that the arm be adjusted in a position that is comfortable for the patient and free from any torsion on the blood vessels. It has been found that a slight abduction of the arm at the shoulder with a slight flexion of the forearm at the elbow and with the hand in the "handshake" position with complete relaxation of the muscles of the entire extremity is the best position for study of the finger tips.

Special Preparation of Patient.—No special preparation of the patients is required for the studies. It is better that they refrain from smoking and the use of alcohol or drugs for a time sufficiently long to ensure that these agents will not influence the blood vessels. The same is true for food or fluids. Essentially the same precautions should be employed that are generally accepted for recording the electrocardiogram. Special periods of fasting and basal conditions are not necessary.

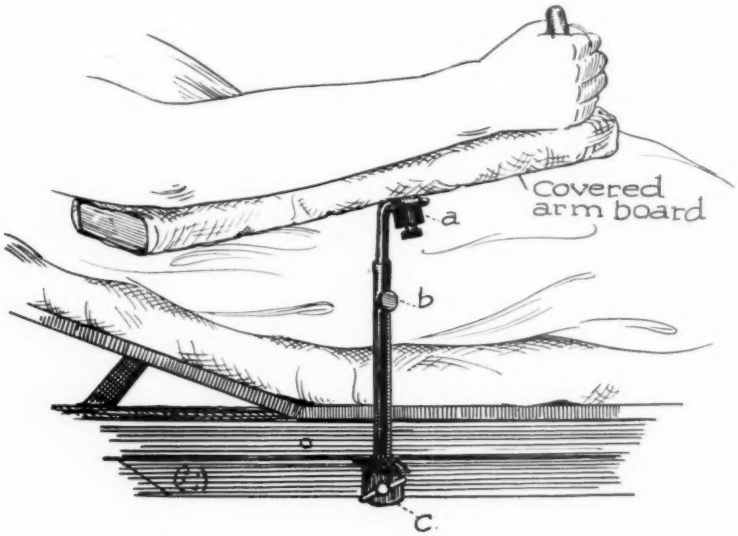


Fig. 11.—The type of arm rest used for study of the finger tips. It is constructed so as to permit adjustments in three directions, thus enabling the part to be brought to heart level and at the same time ensure a comfortable position for the arm.

Measuring the Volume of the Part for Study.—The volume of the part for study can be measured with extreme accuracy by means of negative and positive casts of the part.[3,4] Measurements of volume to an accuracy of several cubic millimeters are not necessary except for highly specialized experimental work. For ordinary clinical purposes more practical methods of sufficient accuracy can be employed to measure the volume of the part. Two methods of this sort are used in this laboratory:

1. One method (Fig. 5, *B*) consists of using a cylinder (*b*) made of lucite with a narrow vertical glass tube (*a*) fixed along the outer wall of the cylinder and connecting with its lumen near the base. A millimeter scale (*c*) is placed near the narrow bore tube. The internal diameter of the large cylinder is made of such a size that an increase of 1.0 c.c. in the volume of the liquid contents of the cylinder causes the meniscus in the narrow bore tube to rise 0.5 millimeter. The large cylinder is filled about three-fourths full with water. A detergent such as octyl alcohol is placed over the fluid in the narrow tube in order to prevent the meniscus from sticking. To measure the volume of the part, the entire part

to be enclosed in the extremity cup is submerged in the water within the large cylinder. For example, if the tip of the index finger is to be studied, the tip of the finger is gently submerged into the water in the large cylinder until the level of the water in the large cylinder reaches the level of the major dorsal and palmar skin creases. The linear rise of the meniscus in the narrow tube in millimeters produced by displacing water in the large cylinder determines the volume of the part. Each 0.5 mm. rise is equal to 1.0 c.c. of part. This method is accurate to 0.2 cubic centimeter.

2. Another method (Fig. 5, *A*), accurate to about 0.1 c.c. and just as simple to employ, follows. The large vessel (*a*), placed on a horizontal platform, is filled with water until it overflows into the calibrated (Esmarch) test tube, (*b*). The part to be studied is then gently inserted into the water until the part to be included in the extremity cup is submerged. The water displaced spills into the calibrated test tube and is equal to the volume of the portion of the extremity to be studied.

Connecting the Part to the Plethysmograph.—An extremity cup is selected that fits the part snugly without constricting the part. This is ensured by providing many cups from which to select. The diaphragm through which the part is inserted is shaped by means of a sharp knife to fit properly. The sealing material (printers' roller compound) is heated in hot water (about 150°F.) until it is of such a viscosity that it may be applied with a wooden applicator around the line of junction between the diaphragm in the cup and the part to make an air-tight seal. The same amount of the part is enclosed in the extremity cup as was measured in the volume-measuring cylinder. After the sealing jelly has stiffened with cooling, the rubber tubing leading from the plethysmograph is connected to the metal tube on the diaphragm of the extremity cup. The rubber tubing is then fixed to the dorsum of the hand or foot with a strip of adhesive tape and then fixed again to the forearm or leg. *When the extremity cups are being connected to the parts, the opening and closing valves should be turned to "open."* This connects the pneumatic system to the atmosphere and protects the sensitive metal capsule while the part is being connected to the instrument. This precaution is exceedingly important. By simply turning the valve to the "closed" position, this isolates the pneumatic system and part from the atmosphere at atmospheric pressure. The part is now ready for testing.

Testing for Leaks.—When the pneumatic system is closed off from the atmosphere, the string shadow can be brought into any position with the baseline adjustment (Fig. 6, *16*). It will not remain in a chosen position if there are leaks. When the pneumatic system is opened to the atmosphere, the string will suddenly return to the original resting position.

Standardization of the String.—After the part has been connected for study, the selector control (Fig. 6, *18*) is properly set and the valve for that part is "closed." The string shadow is then brought to the desired position with the baseline adjustment (Fig. 6, *16*). If this is impossible, then there is a leak

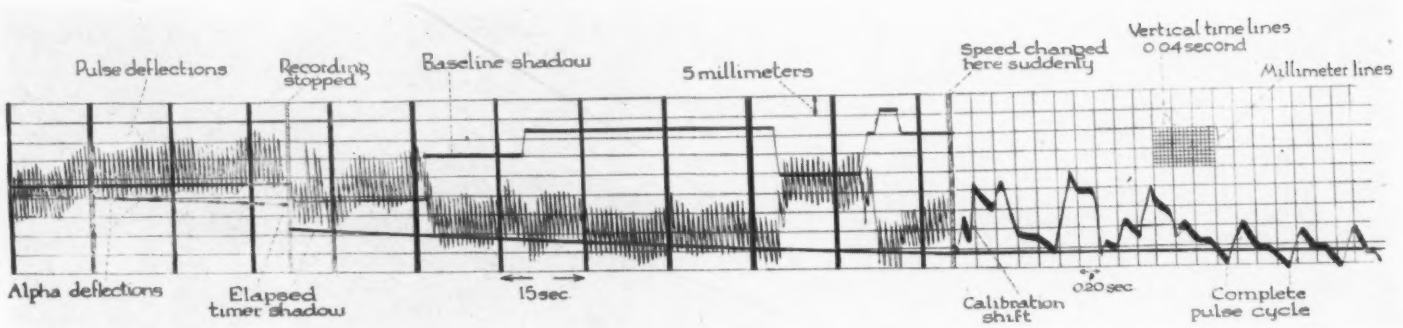
which is usually at the jelly seal at the extremity cup. The string shadow is then focused with the focusing nut (Fig. 6, *19*). By pressing on the calibrator lever (Fig. 6, *23*) and moving it until it is stopped, a 10.0 c. mm. change in volume is produced. From the already measured volume of the part the string shadow is adjusted in sensitivity until its sensitivity is such that a 10.0 mm. movement of the string shadow occurs per 10.0 c.mm. volume change per 5.0 c.c. of part. Table I indicates the necessary linear movement for the string shadow for various-sized parts. As a result of such a standardization, each millimeter movement of the string shadow on the completed plethysmogram is equal to 1.0 c.mm. change in volume per 5.0 cc. of part. This corrects for variations in size of the part and also eliminates any calculations to reduce recordings to a common unit of measurement. This also makes it possible to read quantitatively the plethysmogram directly.

Taking the Plethysmogram.—Once the proper standardization has been completed, the plethysmogram may be recorded. *The string shadow should be brought to the center of the camera slit at the commencement and the termination of the recording.* This ensures more accurate measurement of gross changes in volume. During the recording of the plethysmogram, the calibrator lever (Fig. 6, *23*) should be deflected so as to make an associated record of the standardization for future reference and check. The recording should be made for three or four minutes (longer periods are required to study *gamma* deflections) at the slow camera speed; that is, with the speed change control (Fig. 6, *22*) at the *S* position. Should the string shadow tend to move away from the camera slit, it should be returned by means of the baseline adjustment knob (Fig. 6, *16*). In order to facilitate the interpretation of the completed plethysmogram, baseline adjustments should be used as infrequently as possible. The string shadow should be allowed to move back and forth spontaneously. If the patient is properly relaxed, baseline adjustments are used relatively little unless the patient is subjected intentionally to a stimulus. It is advisable to terminate each recording with a few seconds of recording at the fast camera speed; that is, with the speed change control (Fig. 6, *22*) at the *F* position with one or two associated calibrator lever deflections. This provides an opportunity of studying the morphologic characteristics of the pulse tracing.

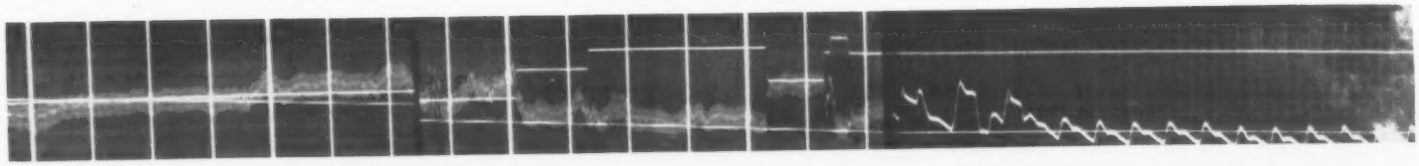
Once the recording has ended, *open all valves to the "open" positions before disconnecting the tubing from the extremity cup.* This protects the sensitive metal capsule which activates the string.

THE PLETHYSMOGRAM

The *plethysmogram*, the completed record of the plethysmograph, is essentially an ordinary type of Cartesian coordinate in which *volume is represented on the ordinate* and *time on the abscissa.* Fig. 12 shows diagrammatically the various configurations of the data recorded on the plethysmogram. The horizontal millimeter lines and the vertical time lines shown for the rapid camera speed are similar to those employed in clinical electrocardiography. In slow speed records,



A.



B.

Fig. 12.—*A* is a drawing of a segment of the plethysmogram shown in *B*. The labelling of *A* is self-explanatory. It can be seen from these plethysmograms that the *pulse deflections* and *alpha deflections* (the more rapid deflections) are recorded by the bowstring. The *baseline shadow* records gross changes in volume of the part, such as large *beta deflections* and *gamma deflections* and is produced by the pin shadows activated by the base-line adjustment. At the fast speed the configurations of the pulse waves are made evident. It can be seen that when the camera was stopped or turned off for the first time, the elapsed timer shadow had shifted 6 mm. in position by the time the camera had been turned on again. This shift represents a 1.5 minute elapse in time. This elapse timer makes it possible to keep a record of time even when the camera is turned off. Consult the text for further details.

the time lines occur at fifteen-second intervals with each fourth time line being broader than the others. This facilitates the counting of whole minute intervals of time. Fig. 12 also shows the sensitive string shadow with a pulse wave for each heartbeat. The slow speed record shows the volume of the *pulse wave* very well without detail configurations of this wave. The fast speed record depicts the details of the pulse wave very clearly. Figs. 12 and 13 also show the *alpha waves* or *deflections*, *respiratory deflections*, and *beta deflections*. Portions of *gamma waves* are being traced by the pin shadows of the baseline adjustment or "coarse recorder." The various types of spontaneous variations in volume of the part are discussed later and are shown in Fig. 13. It is seen from Fig. 12 that

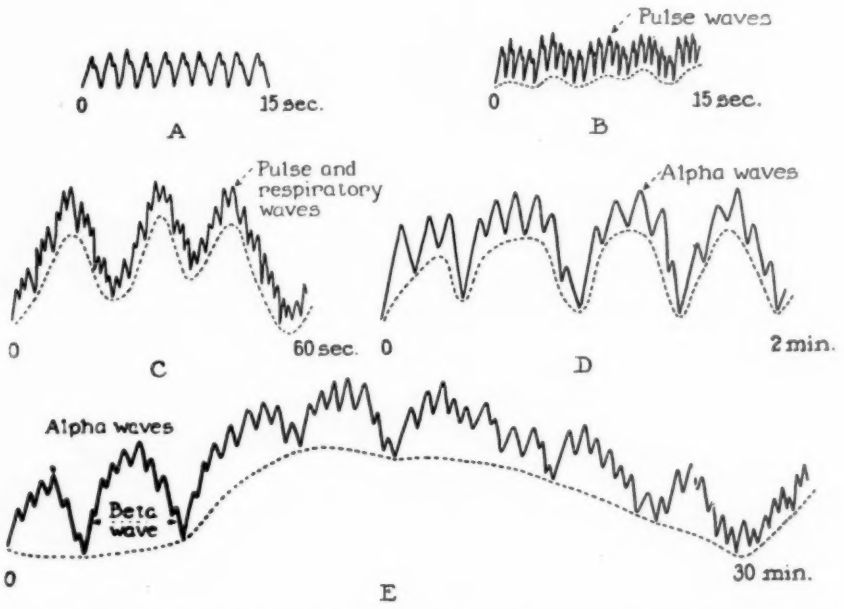


Fig. 13.—Diagram of the five types of spontaneous volume deflections studied to date. They are described in detail in the text.[9] (From Burch, G. E., Cohn, A. E., and Neumann, C.: Am. J. Physiol. **136:** 433, 1942.)

whenever the string shadow is changed to a new position by the baseline adjustment, there results a sudden simultaneous change in the position of the string shadow and the pin shadow of the *baseline adjustment*. The baseline indicator rises in the record when an increase in total volume of the part necessitates an adjustment in the baseline and vice versa. The baseline indicator is seen to draw a graph of gross change in volume of the part. The record, therefore, notes sudden small changes in volume of the part (the string record) and any simultaneous large changes in volume of the same part (baseline indicator).

Since the baseline adjustment or gross volume tracing records volume change (1.0 mm. linear movement per cubic millimeter of volume change) regardless of the size of the part under study, it is necessary to reduce the gross

volume change to the standard unit: cubic millimeter of volume change per 5 c.c. of part. This is very simple to do by merely properly labelling the units on the ordinate axis or vertical axis of the completed plethysmogram. The standardization chart shown in Table I can be used for this purpose and thus eliminate the necessity of any calculations. For example, if the part under study has a volume of 3.8 c.mm., then every 10 mm. on the completed plethysmogram is marked off and labelled 13.2 c.mm. (Table I), since each 10 mm. linear change is equal to

TABLE I. FACTORS FOR CORRELATING MOVEMENT OF STRING WITH VOLUME OF PART

In order to have a completed record in which the size of the part is reduced to a common denominator, the sensitivity of the string is varied. The resultant tracing in millimeters is equal to cubic millimeters per 5 c.c. of part. The factors for calibrations are shown. To perform this, the sensitivity of the string is adjusted so that a complete deflection of the calibrator lever produces the indicated linear movement for the various-sized parts.

VOLUME OF PART (C.C.)	MILLIMETERS STRING SHADOW MUST MOVE	VOLUME OF PART (C.C.)	MILLIMETERS STRING SHADOW MUST MOVE
1.0	50.0	5.2	9.6
1.2	41.7	5.4	9.3
1.4	35.7	5.6	8.9
1.6	31.3	5.8	8.6
1.8	27.8	6.0	8.3
2.0	25.0	6.2	8.1
2.2	22.7	6.4	7.8
2.4	20.8	6.6	7.6
2.6	19.2	6.8	7.4
2.8	17.9	7.0	7.1
3.0	16.7	7.2	6.9
3.2	15.6	7.4	6.8
3.4	14.7	7.6	6.6
3.6	13 9	7.8	6.4
3.8	13.2	8.0	6.3
4.0	12.5	8.2	6.1
4.2	11.9	8.4	6.0
4.4	11.4	8.6	5.8
4.6	10.9	8.8	5.7
4.8	10.4	9.0	5.6
5.0	10.0		

13.2 c.mm. change in volume per 5.0 c.c. of part. The *elapse time indicator shadow* records time that has elapsed during an observation whether the camera is on or off. For example, in Fig. 12, the camera is known to have been turned off during the recording for a period of 1.5 minutes since the elapsed time indicator line moved 6 mm. (4 mm. of movement is equal to sixty seconds) between the time the camera was stopped and started again. The four pins make a complete revolution every hour. Therefore, when the camera is off for continuous periods longer than one hour, one needs only to know the number of whole hours that the camera has been off; periods less than an hour can be calculated from the record.

THE INTERPRETATION OF THE PLETHYSMOGRAM

The plethysmogram is a record of the changes in volume of the part enclosed in the extremity cup in relation to time. The volume changes for the usual periods of time of recording must be due to fluctuations in volume of at least three types of fluid:

1. Blood within the blood vessels
2. Inter- and intracellular fluid
3. Lymph within the lymphatics

In the average patient with the part at heart level it is quite unlikely that variations in volume of the inter- and intracellular fluid contribute very much to the changes in volume except of a special type and under special circumstances[5] (vide infra). From the behavior of lymphatics it is quite likely that variations in the lymph volume of the part do contribute to the waves or volume deflections of relatively slow frequency[5,6] (vide infra). In the main, variations in volume of the blood within the part are responsible for the changes in volume of the part. This blood is contained in many kinds of blood vessels: small arteries, arterioles, capillaries, venules, small veins, and arteriovenous shunts of many sorts, including the highly specialized glomus bodies. The volume changes recorded on the completed plethysmogram are the algebraic summation of many volume changes occurring in various degrees and directions in many different portions of the enclosed part. These volume changes are brought about by the integration of many hemodynamic, or physical, chemical, psychoneurogenic, and other physiologic phenomena. The entire process which results in any type of change in volume of a highly specialized organ such as the finger tip is concerned with many complicated and little-known local and systemic physiologic processes. The exact role of the various types of blood vessels in the production of the volume changes is not known. From the present state of knowledge of the function of the various types of peripheral blood vessels, certain functions of each of these is known in general terms only. These generally accepted concepts of function for each of the previously mentioned vessels are applied to the interpretation and application of the plethysmogram with similar precision. A precise interpretation cannot be offered, but many valuable facts have been established. The field for study

is quite fruitful and deserves considerable investigation; in the past it has been limited by inadequate standard methods and apparatus for study.

At the present time certain facts have sufficient importance to warrant discussion.

A. Types of Spontaneous Variations in Volume of the Part

If a patient rests quietly in bed in a comfortable environment as described previously, spontaneous changes that occur in the volume of the part result in at least five types of *deflections*. They are (1) pulse waves or deflections, (2) respiratory deflections, (3) alpha deflections, (4) beta deflections, (5) gamma deflections.

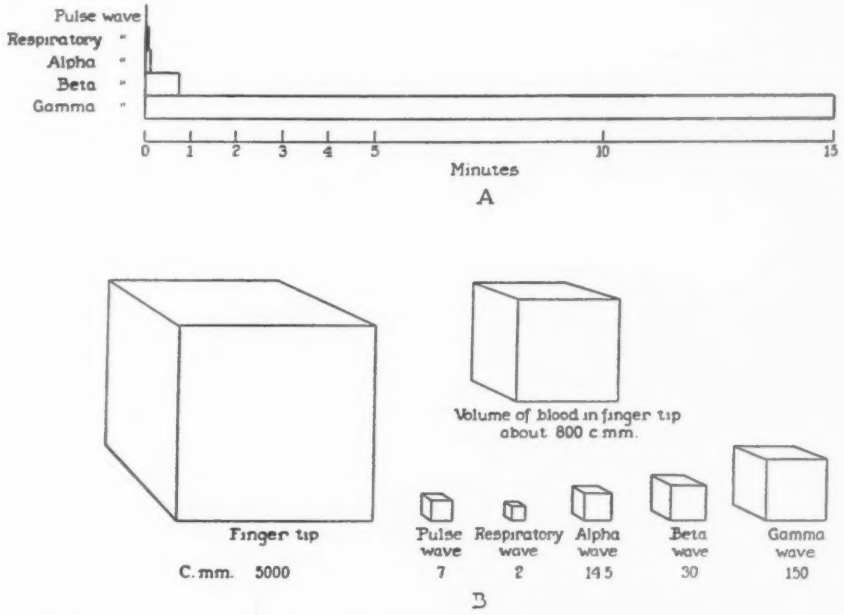


Fig. 14.—Diagrammatic representation of the mean time and volume values of spontaneous volume deflections for the finger tip of the normal adult at rest in a comfortable room.[9] (From Burch, G. E.: Cohn, A. E., and Neumann, C.: Am. J. Physiol. **136:** 433, 1942.)

These volume deflections have been described in detail elsewhere by Burton,[7] Hertzman and Dillon,[8] and Burch, Cohn, and Neumann.[9-11] They are illustrated diagrammatically by Figs. 13 and 14. The spontaneous changes that occur in the tips of the fingers and toes range from less than 0.1 to 350 c.mm. or more per 5.0 c.c. of part.* The recognizable volume deflections are as follows:

1. *Pulse Waves or Deflections.*—These are occasioned by the heartbeat and their volume varies markedly (Figs. 12, 13, and 14). There is a definite relationship of volume of the pulse to the alpha wave. The variations in volume

*Henceforth volume changes in a part are given as cubic millimeters per 5 c.c. of part.

for the normal are given in Table II. The mean volumes were 6.9 c.mm. in the finger tips, 4.0 in the toe tips, and 4.1 in the pinnae. The frequency of the pulse deflections varies with the heart rate.

2. *Respiratory Deflections.*—Variations in volume occur with the respiratory cycle (Figs. 12 and 15). They are most highly developed in the pinnae and least developed in the toes. Their rates vary with the respiratory rate. In the normal subject, their volume varies from less than 0.1 to 5.0 cubic millimeters.

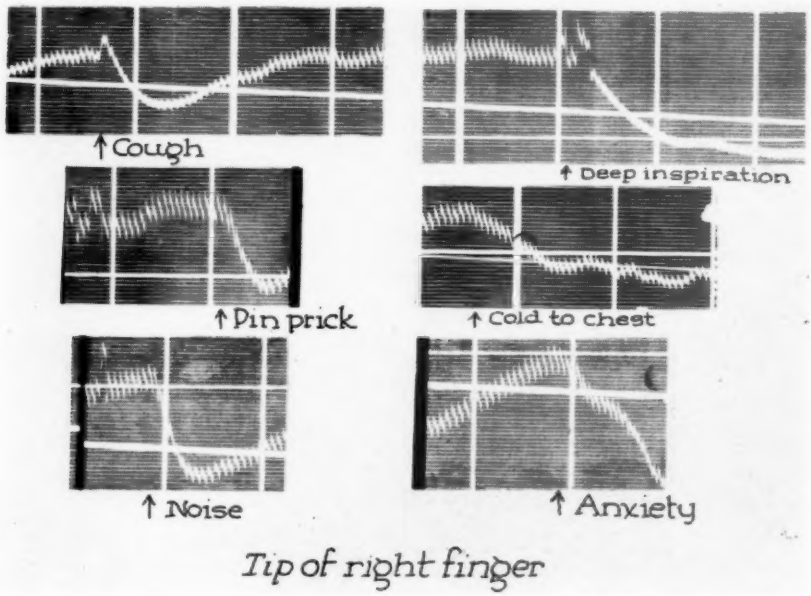


Fig. 15.—Plethysmograms showing vasoconstriction brought about by various stimuli. The first two (cough and deep inspiration) are intrinsic neurogenic stimuli, the second two (pin prick and cold) are extrinsic neurogenic stimuli, and the last two are extrinsic psychogenic stimuli. The anxiety stimulus was brought about by informing the subject, a student, that he had failed a recent examination. These reactions demonstrate the sensitivity of the small peripheral blood vessels to stimuli as well as the potential value of the plethysmograph in the study of neuropsychogenic phenomena. These plethysmograms were recorded at slow camera speed.

A special type of respiratory deflection occurs in the fingers and toes within a few seconds after a deep inspiration. It may present several characteristics:

(a) Following a deep inspiration, there results a spontaneous sudden decrease in volume of the part which is not dependent upon external stimuli (Fig. 15). This varies from 5.0 to 105 cubic millimeters. Associated with this over-all decrease in volume there is a decrease in volume of the pulse waves. After a few pulse beats, vasodilatation begins and continues until the previous pulsatile characteristics are reached. A series of small (2.0 to 8.0 c.mm.) alpha waves appear before the vasodilatation is complete.

(b) The volume changes are more prominent in the fingers than in the toes.

(c) After two or more successive deep inspirations, the degree of response diminishes until no response follows—a sort of tachyphylaxis. The shorter the interval between the deep inspirations, the less the volume change.

(d) The change in the pinnae is not as definite and predictable nor as large as in fingers and toes, nor is it necessarily concordant. There may be either an increase or a decrease.

3. *Alpha Deflections.*—Volume changes less frequent than respiratory deflections are called alpha deflections (Figs. 12, 13, and 15). They are present in all parts and in all people. They vary in frequency and size. They are not uniform, although the contours of the deflections may be smooth. The mean frequency of the deflections is 15.8 per minute in the finger tips, 15.4 in the toes, and 17.2 in the pinnae. The mean volume of the deflections are, respectively, 14.5, 7.1, and 6.6 c.mm. for each part. The variations are shown in Table II, the minimum being less than 0.5 c.mm. and the maximum as great as 81 cubic millimeters. No correlation between frequency and volume necessarily exists.

The volume of the alpha deflections tends to vary in different individuals. These variations and correlations with the pulse waves and the state of the person are discussed below. The alpha deflections are not dependent upon variations in arterial pressure.[9,12] Sympathectomy or sympathetic nerve blocking will inhibit alpha deflections almost entirely. The alpha deflections in the fingers, toes, and pinnae do not necessarily vary concordantly.[11]

TABLE II

Quantitative characteristics of the pulse and alpha deflections for the finger tip, toe tip and postero-superior portion of the pinna of twelve resting normal white adults varying from 22 to 65 years of age. Five were women. The room conditions were comfortable.

	VOLUME OF THE DEFLECTIONS OF THE ALPHA WAVES (C.MM. PER 5 C.C. OF PART)		FREQUENCY OF THE DEFLECTIONS OF THE ALPHA WAVES (NUMBER PER MINUTE)			VOLUME OF THE PULSE WAVES (C.MM. PER 5 C.C. OF PART)		
	MEAN	MAXIMUM	MEAN	MAXIMUM	MINIMUM	MEAN	MAXIMUM	MINIMUM
Finger tip	14.5	81.0	7.9	14	2	6.9	12.4	0.9
Toe tip	7.1	43.4	7.7	13	2	4.0	11.5	0.7
Pinna	6.6	21.0	8.6	13	2	4.1	10.5	0.9

4. *Beta Deflections.*—The succession of alpha waves is superimposed upon large deflections called beta deflections (Figs. 13, 14, and 16). The frequency of these deflections is one to two per minute and the size, 5.0 to 60 cubic millimeters. Beta deflections are exhibited in all parts. Their frequency and volume are totally irregular but tend to vary concordantly in the fingers, toes, and pinnae.

5. *Gamma Deflections.*—These are slowly developing deflections that may reach extensive changes in volume (Figs. 13, 14, and 17). They vary from about one to eight deflections an hour and their size, from about 50 to 350 cubic millimeters. They tend to vary concordantly in the fingers, toes and pinnae, but there is not necessarily a constant relationship.

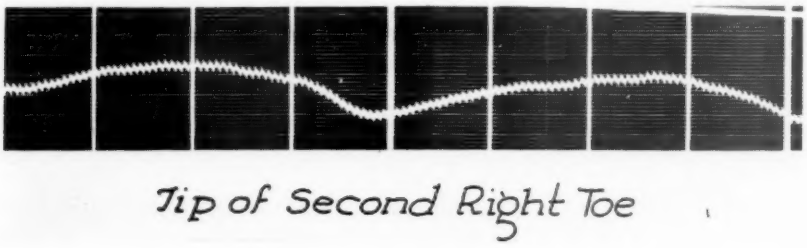


Fig. 16.—Two complete *beta waves* or four *beta deflections.*

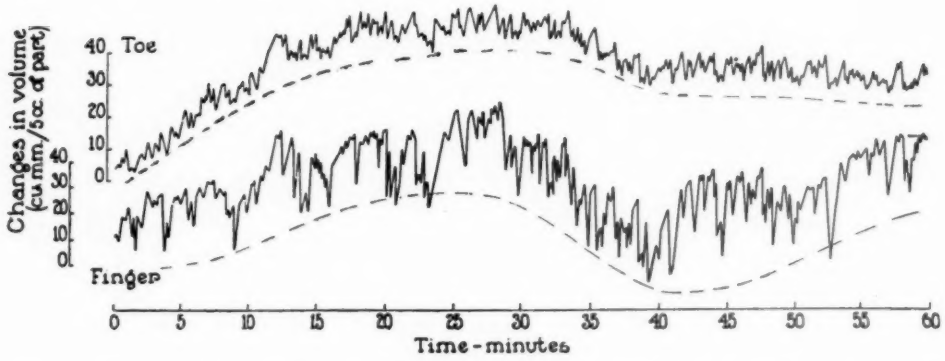


Fig. 17.—Diagrams of a continuous tracing of *alpha*, *beta*, and *gamma* deflections.[9] (From Burch, G. E., Cohn, A. E., and Neumann, C.: Am. J. Physiol. **136:** 433, 1942.)

The deflections are superimposed upon the next slowest type of deflection. There is at least another deflection of a frequency slower than that of the gamma deflection. It has not received any intensive study.

During the course of prolonged studies, variations in room temperature may change the volume of the air within the extremity cup. To study quantitatively the deflections of slow frequency, the room temperature must be controlled. Perspiration occurs at an almost uniform rate under comfortable environmental conditions and therefore only shifts the baseline at a uniform rate without distorting the volume deflections described in the foregoing.

B. Normal Variations in the Plethysmogram

When the subject is resting quietly and comfortably and is relaxed mentally, the pulse and alpha deflections present the normal values of volume and frequency previously described. There are marked variations which can occur

within the normal under certain circumstances which deserve special comment. During some of these conditions the plethysmogram can resemble that found in diseased states and therefore must be adequately appreciated. The discussion below will be mainly limited to the pulse and alpha deflections because only they have received a significant degree of evaluation. The beta and gamma deflections will be mentioned rarely.

Psychic State.—The psychic state of the individual can influence the pulse and alpha deflections greatly (Fig. 15). When the patient is tense, anxious, unhappy in his environment, frightened by the study, or in any way ill at ease, the pulse and alpha deflections will tend to be small in volume and the rate of the pulse deflections is increased by the tachycardia. This type of reaction is due to the increase in vasomotor tone associated with the increase in sympathetic activity related to the psychic disturbance.

Changes in the patient's state of mental tension are reflected by changes in the character of the spontaneous volume deflections. Measurements of these changes may serve[9-13] as a means of evaluating, in part at least, some aspects of the psychic state of an individual. With flushing or blushing there results a marked increase in the volume of the pulse deflections and an associated decrease in the volume of the alpha deflections. When the patient is comfortable and relaxed and the vascular tone is of an average normal amount, the pulse deflections are of moderate or mean volume and the alpha deflections are of good volume.

Cold.—When the patient's body is chilled by a cool room, or by applying cold locally to any portion of the body, there results a vasoconstriction with a marked reduction in the volume of the pulse and alpha deflections (Fig. 15). The degree of vasoconstriction is more or less proportional to the degree of chilling. Cold is a strong vasoconstrictor stimulus and can be employed as a test of an intact neurovasomotor mechanism. After prolonged chilling, vasodilatation may set in with a resultant increase in volume of these deflections; as a rule the alpha deflections increase in volume to a relatively greater degree than the pulse deflections. Because of the profound influence of chilling upon these deflections, it is necessary to control this factor by making certain that a previously chilled patient has warmed and is comfortable in the room atmosphere. It is well to remember that when there are relatively slight drafts, a resting individual may be chilled even though the dry bulb temperature is within a comfortable range.

With prolonged chilling, the volume of the finger and toe tips decrease slowly and definitely and result in a negative gamma deflection; that is, an over-all decrease in volume of the part. When the part warms again and blood accumulates to restore the blood volume within the part to its original level, a positive gamma deflection is recorded; that is, there is an over-all increase in volume of the part.

Heat.—When the patient's body is heated by a hot room or by applying heat locally to any portion of the body, there results a marked increase in volume

of the pulse deflections with a marked reduction in the alpha deflections (Fig. 18). There is a gradual increase in over-all volume of the part with the inscription of a positive gamma deflection. These changes are the result of marked vasodilatation with an increase in the volume of the local blood "reservoirs" (probably a misnomer). When the body is cooled to basal levels again, the deflections return to normal.

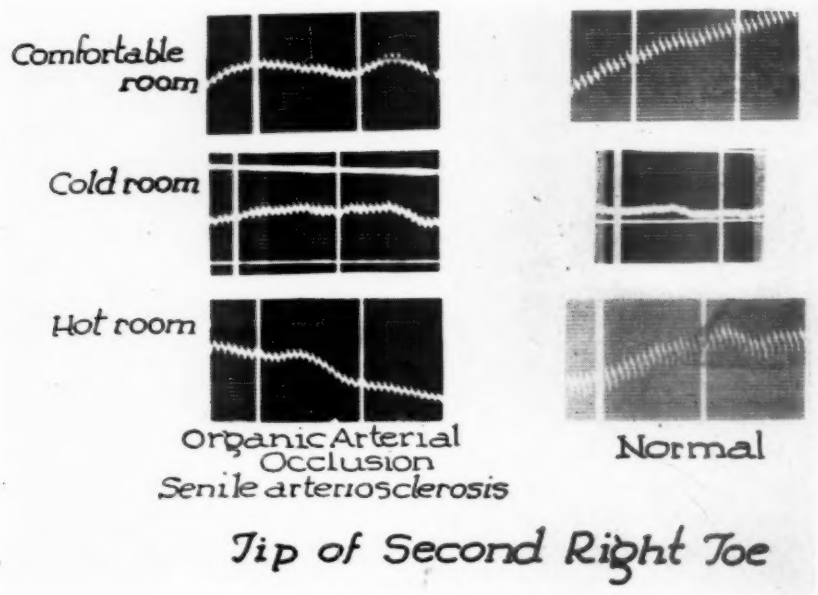


Fig. 18.—An illustration of an isolated use of the plethysmogram in the diagnosis of organic arterial occlusion (obliterating senile arteriosclerotic endarteritis). The volume of the pulse deflections in the comfortable room is considerably less than the normal shown to the right. In the cold room there was a marked vasoconstriction in the normal, evidenced by the marked reduction in size of the pulse deflections. There was only a very slight reaction in the patient with organic arterial occlusion. When the room atmosphere was made very warm to produce vasodilatation, there was essentially no change in the size of the pulse deflections. This indicates a failure or inability to increase the blood flow to the part. On the other hand, the normal subject showed a marked vasodilatation under the influence of the hot room. Such an environment is very strong vasodilatation stimulus. Such a combination of reactions indicate *organic arterial obstruction*, a *fixed circulation*, and a marked impairment of the *peripheral circulatory reserve*. Consult the text for further details of the use of the plethysmogram in disease.

These reactions serve as a good test for organic occlusive arterial and arteriolar disease (Fig. 18). In the presence of occlusive arterial disease, as thromboangiitis obliterans or obliterating arteriosclerotic endarteritis, such vasodilating reactions are impaired or absent (vide infra). The application of heat (45°C.) locally to the torso or to an extremity to produce vasodilatation in the finger or toe tip of another extremity not only tests the patency of the arteries and peripheral blood vessels to that extremity, but also tests the neurovascular reflex mechanism to the part. This is a very useful test clinically for the evaluation of sympathetic activity.

Deep Inspiration.—The vasoconstriction following deep inspiration was described previously when the respiratory deflections were discussed.

Relation of the Part to Heart Level.—When the part is placed below heart level, the volume of the pulse and alpha deflections decrease.[14] The greater the distance below heart level, the greater the decrease in volume of these deflections. As the force of gravity results in the pooling of blood and lymph in the dependent part, a positive gamma deflection is inscribed. The decrease in volume of the pulse and alpha deflections occurs gradually and apparently in direct proportion to the filling of the vessels within the part. The mechanism for the decrease in volume of the pulse deflections remains unknown. Arteriolar vasoconstriction may be a contributing factor. A significant factor is the distention of the vessels with a decrease in further distensibility of the vessel walls.

When the part is elevated above heart level, the volume of the pulse deflections increases markedly and a negative gamma deflection results as the blood within the part drains out. The effect of gravity on the vessels is just the opposite of that produced by lowering the part below heart level. Because of these reactions, it is preferable to keep the part at or near the level of the heart during recordings.

Sympathetic Procaine Block.—Blocking of the sympathetic nerve supply to a finger or toe tip results in a marked increase in the volume of the pulse deflections with an almost complete elimination of the alpha deflections. During the early phases of the interruption of the sympathetic innervation there results an engorgement of the vessels within the part with a resultant positive gamma deflection. The loss of the alpha deflections is to be expected since they are concerned with variations in sympathetic nervous activity.

The use of sympathetic nerve blocking is another important test of arterial patency. Occlusion of the lumen of arteries by organic disease results in an impairment or loss of vasodilatation response to block of the sympathetic innervation to the part.

The finding of vasodilatation following the block of sympathetic nervous pathways in the presence of vascular disease is no indication *ipso facto* that sympathectomy is the therapeutic procedure of choice. In fact, the criteria for the choice of sympathectomy in therapy have never been satisfactorily established.

C. The Plethysmogram in Certain Types of Vascular Disease

The plethysmogram for several types of vascular diseases will be described briefly. A more extensive and detailed discussion is to be reported later.

Obstructive Arterial Disease.—In occlusive diseases of the arteries, such as thromboangiitis obliterans or obliterating arteriosclerotic endarteritis, the volume of the pulse and alpha deflections are reduced (Fig. 18) in proportion to the degree of occlusion of the arteries. In some instances the occlusion may be so complete as to reduce the volume of the pulse deflections to zero. The alpha

deflections are present but markedly reduced in volume and frequency unless there is a complete absence of circulation to the part. Of further diagnostic significance is the reduction in the degree of vasodilatory response to heating the body (generally or locally) or to sympathetic blocking. When the occlusive disease is extensive, there may be no vasodilatation following heating or sympathetic blocking (Fig. 18). The degree of vasodilation (evidenced by the increase in volume of the pulse deflections) following sympathetic nerve block with procaine is an index of the degree of immediate response that may be expected after sympathectomy.

When the occlusive disease is the result of vasospasm or is functional in nature, the pulse and alpha deflections show the same type of change as in organic occlusive disease. However, heating the body or blocking the sympathetic nerves produces a definite and marked vasodilatory response. During the periods between the vasospasm, the alpha and pulse deflections have a normal appearance. This is well exemplified by Raynaud's phenomenon. During the period of syncope or marked arterial spasm there are no pulse and only small alpha deflections, but these return to normal when the spasm is released.

As yet the knowledge of the plethysmogram has not developed to a stage where types of organic or functional occlusive arterial diseases can be differentiated from various entities within each of these two groups. For example, it is not possible to make a diagnostic differentiation between extensive thromboangiitis obliterans and obliterative arteriosclerotic endarteritis merely on the basis of the plethysmogram. It is quite likely that the plethysmograms in these two conditions are entirely different but, with the limited data available at present, no such differentiation can be made.

Vasospastic Peripheral Vascular States.—There are a number of vasospastic states which frequently confront the clinician and must be differentiated. The most frequent one results from anxiety states, simple apprehension, emotional disturbances, and other psychogenic phenomena. These result in small pulse deflections and relatively small alpha deflections. By merely comforting the patient and inducing him to relax by properly discussing his problems, his pulse and alpha deflections return to the average normal values. By a properly arranged observation room,[2] these vasospastic phenomena can be controlled much more easily. Should difficulty arise in relieving the vasospasm, heating the subject will result in a release.

Vasospastic states or organic vascular diseases associated with vasospastic crises, such as Raynaud's phenomenon, are also characterized by small to absent pulse and alpha deflections; the pulse deflections especially are small. This vasospasm is released by slow local or general heating of the part or body and by sympathetic procaine block. The volume of the pulse and alpha deflections then increase. The sympathetic tone is not necessarily increased above normal in Raynaud's disease. As mentioned previously, such testing differentiates organic obstructive disease from obstruction due to vasospasm.

Arterial Aneurysms.—With the development of an aneurysm of one of the main arteries to a limb, the pulse and alpha deflections are reduced in volume in the digits of the part. The size and nature of these deflections indicate the adequacy of the circulation. The plethysmogram is a better index of the adequacy of the collateral circulation to the part than the oscillometer, for example. Although the plethysmogram will show a reduction in the pulse and alpha deflections of the index finger of the side with an aneurysm, the volume deflections may be fairly good and indicate adequate circulation. On the same patient oscillometric recordings have shown an absence of pulsations in the involved limb. Ligation of the artery proximal to the aneurysm in such a patient has resulted in a clinical cure without untoward peripheral vascular effects.

Thrombophlebitis, Venous Obstruction, and Increased Venous Pressure.—With an increase in venous pressure, regardless of its cause, there is an inverse relationship of the venous hypertension to the volume of the pulse and alpha deflections. The decrease in the volume of these deflections is probably related to a decrease in distensibility of the peripheral vessels as a result of the stretching of their walls by the increased venous pressure and, in some part, to arteriolar constriction. Although the former is more important when the venous pressure is markedly elevated, the relative roles of the two are unknown. Heating the body or sympathetic procaine blocking will release the vasospasm. The amount of release is indicated quantitatively by the degree of increase in volume of the pulse and alpha deflections. The degree of this response is an index of the degree of the immediate clinical vascular response to be expected from sympathetic nerve block or sympathectomy in these conditions.

Miscellaneous Clinical States.—As mentioned at the onset of the discussion of the plethysmogram in vascular diseases, detailed discussions will be published in the near future. Nevertheless, a few more miscellaneous vascular diseases in the clinical management of which the plethysmogram plays a role are:

(1) *Senility*: In the absence of occlusive arterial disease due to arteriosclerosis, uncomplicated senility is usually associated with a slow frequency and large volume of the pulse deflections and relative small volume changes in the alpha deflections. These deflections have been described previously for senility.[15]

(2) *Diastolic Hypertension*: This condition tends to be associated with small pulse deflections and fairly well-developed alpha deflections. There are marked variations with considerable overlapping of the normal. The values in several types of diastolic hypertension have been described by Burch, Cohn, and Neumann.[15]

(3) *Psychoneurotic States*: Neumann and associates[13] undertook to employ the plethysmograph in an analysis of the peripheral vascular behavior in emotional states. They found the plethysmogram to vary with the emotional states in a manner which strongly indicates its value in clinical psychiatry.

SUMMARY

A new portable plethysmograph is described which is all metal and, therefore, sturdy and free from the difficulties of deterioration—an important problem when rubber membranes are employed. A device for standardization is incorporated which makes it possible to correct for finger and toe size, thereby resulting in a completed plethysmogram which can be read directly from subject to subject and from time to time in the same subject. This eliminates calculations usually required to convert volume changes to standard units. The plethysmograph also contains a master elapse time recorder which makes it possible to record time even when the camera is off. By means of a baseline adjuster and recorder, gross or large and slow variations in volume of the part can be recorded.

The completed plethysmogram is discussed and five types of spontaneous deflections in volume are considered. The plethysmogram shows the volume changes at slow and fast speeds. The former makes it possible to study all five types of spontaneous deflections in volume, while the latter makes it possible to study the configurations of the pulse wave in detail.

A discussion of the methods of recording the plethysmogram, precautions and possible errors in recording, and its interpretation are given. The use of plethysmography in the study of peripheral vascular disease, psychogenic states, and states of relaxation and tension are briefly indicated. Detailed applications of the plethysmogram to normal and abnormal clinical states will be presented in the near future.

This plethysmograph is a new instrument which is objective, precise, simple, and practical. It has great promise in the study of many problems in health and disease which manifest themselves by disturbances in the blood vessels, lymphatics, and intercellular and intracellular and fluid volumes of the tips of the fingers and toes. By far the greatest number of experimental and clinical applications remain unknown. As with the introduction of any new instrument which has applications in the biologic fields generally and broad use in these fields, the science is in its infancy. It is only with the patient efforts of many investigators, both in the laboratory and the clinic, that the plethysmograph and plethysmogram will develop and reach a state of adequate evaluation and proper usage.

Appreciation is expressed to Mr. G. Morgavi for his technical assistance and excellent machine work which contributed considerably to the development of the plethysmograph.

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FATAL CORONARY ARTERY DISEASE IN YOUNG MEN

CAPTAIN WILLIAM D. POE
MEDICAL CORPS, ARMY OF THE UNITED STATES

CORONARY artery disease is not generally believed to be a frequent cause of death in people below the age of 40 years. The purpose of this commication is to present nine cases, taken from the records of one Army hospital, of fatal coronary artery disease in young men.

The cases were taken from the protocols of 365 consecutive autopsies, of which 280 were upon patients between the ages of 18 and 40 years. Of these 280 patients, 159 came to autopsy as a result of drowning, trauma, poisoning, shooting, or explosion, a figure much higher than would be expected in the civilian population. The remaining 121 patients died of natural causes. In 7.4 per cent of these 121 patients, autopsy indicated that disease of the coronary arteries was the cause of death. Coronary artery disease accounted for 3.2 per cent of all deaths, including violent deaths, in the 280 patients whose ages ranged from 18 to 40 years.

The cases to be reported are cases in which the only cause of death found at autopsy was disease of the coronary arteries. In no case was coronary disease an incidental finding.

CASE REPORTS

CASE 1.—A 22-year-old soldier was marching in review on June 8, 1942, when he suddenly collapsed and died before a medical officer reached him. A review of his medical record failed to reveal any symptoms suggestive of heart disease. He had never been a patient in this hospital.

Autopsy Findings.—The heart weighed 280 grams. There was no gross abnormality of the myocardium. The anterior descending branch of the left coronary artery contained large, irregular, yellowish plaques throughout its course. These plaques narrowed the lumen of the vessel, most markedly in its proximal portion. Plaques also narrowed the marginal branch of the right coronary artery.

There were numerous plaques beneath the intima of the aorta in its descending portion. The lungs revealed an old scar in the right apex but elsewhere were crepitant in consistency. A moderate amount of frothy blood oozed from the cut surfaces. The liver weighed 1,596 grams and presented no gross abnormality other than slight enlargement.

Microscopically the myocardium showed only cloudy swelling. The coronary arteries revealed marked asymmetrical fibrous thickening and narrowing of the lumina. Cholesterol deposits could be seen in the intima of the vessels. The lungs revealed congestion of the alveolar capillaries, and many of the alveoli were filled with red blood cells and edema fluid. The liver revealed marked congestion of the blood sinusoids.

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CASE 2.—On the morning of Jan. 6, 1943, a 33-year-old soldier went through an obstacle course. Upon finishing, he said to a companion, "Gee, that one got me!" Immediately following this, he fell to the ground and died at once. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 308 grams. The myocardium revealed a number of irregular whitish areas which were most numerous beneath the endocardium of the left ventricle. All of the coronary arteries contained atheromatous plaques which produced varying degrees of occlusion. There was extreme narrowing of the anterior descending branch of the left coronary artery, just distal to its point of origin.

There were a few atheromatous plaques in the intima of the aorta. The liver weighed 2,156 grams but was otherwise unremarkable. On cut section there was oozing of frothy material from the lower lobes of the lungs.

Microscopic sections showed fibrosis, degeneration of muscle cells, and mononuclear infiltration in various areas of the myocardium. There were atheromatous plaques in the coronary arteries which showed evidence of calcification. In some sections the lumina of the coronary vessels were greatly narrowed.

The liver showed fatty infiltration. The alveoli of the lungs showed an infiltration of large, mononuclear, pigment-filled cells.

CASE 3.—A 31-year-old artilleryman was last seen alive at 11:30 A.M., Jan. 21, 1943. At this time he seemed to be in good health. At approximately 3:00 P.M., the post medical inspector was called and found the soldier dead in bed. There had been no recent illness or history of cardiac disease.

Autopsy Findings.—The heart weighed 475 grams. On the anterior part of the left ventricle near the apex an irregular pale area was visible. Throughout both left and right coronary arteries many yellowish plaques could be seen. This process was most marked in the circumflex and anterior descending branches of the left coronary. About 1.0 cm. distal to the origin of the anterior descending branch of the left coronary artery the lumen was completely filled with purplish-gray material which could be separated from the wall of the vessel only with difficulty.

The aorta revealed scattered, small, atheromatous plaques in the ascending and descending portions. The liver weighed 2,320 grams but was otherwise grossly normal.

Microscopic study of the coronary arteries revealed atherosclerosis and almost complete occlusion of the left coronary artery. Sections of the myocardium revealed small foci of degeneration in the outer wall of the myocardium of the left ventricle. In addition there was an extensive infiltration of neutrophiles and a moderate infiltration of histiocytes.

The liver revealed fatty changes. The aorta revealed atherosclerosis.

CASE 4.—A 31-year-old infantryman had been absent without leave for several days prior to his death. He had been drinking heavily for four or five days. On the morning of Feb. 13, 1943, he was found dead in bed. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 364 grams. The cardiac chambers were dilated and filled with fluid blood. In the left main coronary artery just above its bifurcation there was an irregular, thick, firm, white atheromatous plaque which produced almost complete occlusion of the vessel. About 3.0 cm. distal to the origin of the right coronary artery there was a single plaque similar to that in the left coronary artery. No thrombi could be found.

Several small whitish plaques protruded from the intima of the aorta. The ductus arteriosus was patent and would admit the end of a probe about 2.0 mm. in diameter.

The lungs were heavy and boggy, and dark blood and frothy material oozed from the cut surfaces. A small calcified nodule was present on the pleural surface of the lower lobe of the left lung. The liver weighed 2,170 grams and was flabby in consistency. Just beneath the capsule of the anterior part of the right lobe near its anterior border was an irregular, unencapsulated, soft purple area 3 mm. in diameter.

Microscopic examination of the myocardium revealed fragmentation of muscle cells, patchy fibrosis, and a slight infiltration of neutrophiles. Sections of the coronary arteries revealed athero-

sclerosis with calcification which caused marked narrowing of the vessels. Atherosclerosis of the aorta was evident in the microscopic sections.

The lungs revealed marked congestion and many of the alveoli contained large, mononuclear, pigment-bearing cells. The liver revealed fatty changes. In a section made of the small purplish mass many endothelial-lined, blood-filled spaces were seen. This was diagnosed as a hemangiomal

CASE 5.—The history obtained on a 27-year-old soldier was indefinite. Shortly before death, he had been drilling. He was carried to a dispensary, and upon arrival there he was pronounced dead by a medical officer. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 460 grams. The myocardium of the left ventricle was very flabby. In the anterior part of the left ventricle there were many small, irregular, whitish areas, which were more numerous near the endocardial surface. Beneath the endocardium of the posterior portion of the left ventricle were numerous reddish-purple areas which had the appearance of extravasated blood.

There were small sclerotic plaques at each coronary ostium which did not narrow the lumina of the coronary vessels. Numerous large plaques were seen interspersed along the lumina of the larger coronary vessels which narrowed them in many places. Near the origin of the circumflex branch of the left coronary artery the lumen of the branch was filled for a distance of 1 cm. with firm, grayish material. A short distance below the origin of the anterior descending branch of the left coronary artery was a large sclerotic plaque.

The lungs were crepitant and frothy, bloody fluid oozed from the cut surfaces. The liver presented no gross abnormalities and had an estimated weight of 1,500 grams.

Microscopic examination of sections of the myocardium taken from the left ventricle revealed numerous areas of fibrosis. In one section taken from near the endocardial surface, the nuclei of the muscle cells were pyknotic, and the fibers were swollen and pale. In this area there was a marked polymorphonuclear leucocytic infiltration.

The coronary arteries had large atheromatous plaques which narrowed the lumina of the vessels. In a section taken from the completely occluded circumflex branch of the left coronary artery, a recanalized thrombus was evident. Evidence of slight atherosclerosis could be seen in sections of the aorta.

The lungs showed congestion of the capillaries and mononuclear, pigment-filled cells in the alveoli. The liver revealed fatty changes.

CASE 6.—A 34-year-old sergeant was apparently asleep in his barracks on the morning of Jan. 1, 1944. He was heard to gasp and when examined a few minutes later was found to be dead.

Autopsy Findings.—The heart weighed 392 grams. The cardiac chambers were distended with blood. The pericardium over the lower anterior part of the left ventricle covering an area of about 3.0 cm. in diameter was dull and opaque in appearance. The endocardium at a corresponding position was discolored, and the underlying myocardium was yellowish in color and soft in consistency. Throughout the aorta there were numerous sclerotic plaques, and over one of these the endothelium seemed to be absent. This denuded plaque was located in the ascending aorta.

Throughout all of the coronary arteries numerous plaques were present. An especially large plaque nearly obliterated the lumen of the anterior descending branch of the left coronary artery just distal to its origin. Part of this plaque was brownish in color, and opposite it a soft friable blood clot completely obstructed the lumen of the vessel for a distance of about 5.0 millimeters. Just distal to the origin of the right circumflex coronary artery, sclerotic plaques obstructed the lumen. Distal to the plaques the lumen of the vessel was filled with firm, pulpy, purple material which was detached with difficulty.

The lungs were generally crepitant in consistency, and there was a small scar on the surface of the left apex. Blood and frothy material oozed from the cut surfaces. The liver weighed 1,757 grams, and dark blood oozed from the cut surfaces.

Microscopic examination of sections from the left ventricle showed varying degrees of scarring and degeneration. In some areas a slight infiltration of histiocytes and neutrophiles could be seen. The anterior descending branch of the left coronary artery showed marked atherosclerosis with fibrosis of the arterial wall. An organizing thrombus was present in this vessel. A section from the proximal part of the right marginal branch revealed that the lumen was completely filled by dense fibrous tissue in which there was a slight infiltration of mononuclear cells.

The aorta showed a fibrous hyaline plaque beneath which the muscular fibers were degenerated. The lungs revealed only moderate congestion and pigment-filled mononuclear cells in the alveoli. The liver showed congestion of the blood sinusoids and fatty infiltration.

CASE 7.—A 38-year-old infantryman had been in the army fifteen months. During that time he had never been on sick call and had never complained of any symptom referable to the cardiovascular system prior to his last illness. On May 3, 1944, he casually remarked to one of his associates that he was having a little difficulty in breathing at times but that this symptom did not trouble him particularly. On the morning of May 4, 1944, he ate breakfast with his company and seemed to feel well at the time. Following breakfast he went to his barracks and sat down on his bed. At about 7:10 A.M. one of the men in the barracks noted that he was lying on the bed apparently unconscious. He was groaning, and, after a few minutes, vomited several times in quick succession. A medical officer was called, and when he arrived at 7:25 A.M. the soldier was dead.

Autopsy Findings.—The heart weighed 364 grams. No areas of scarring could be observed grossly. The chambers were dilated and contained partly clotted blood. The entire left coronary artery proximal to its division contained a large irregular atheromatous plaque with interspersed zones of calcification. The lumen of this artery was slitlike and could be recognized only by moving the walls of the vessel longitudinally. The anterior descending branch of this artery contained a similar plaque extending along the vessel for 1.5 cm. from its point of origin. No other plaques were seen in the other coronary arteries. Only a few minute yellowish flecks were seen in the aorta.

The lungs were crepitant. Beneath the pleura of the left upper lobe two small nodules 3 mm. in diameter, filled with caseous material, were seen. The lungs were not boggy or scarred, and only a small amount of dark blood oozed from the cut surfaces. The liver weighed 2,100 grams. The cut surface was dark yellowish-brown in color, and blood oozed freely from it.

Microscopic study of sections of the coronary arteries revealed marked atherosclerosis. In the section taken from the left main coronary the intimal surface of the plaque was seen was to be absent. A small fresh thrombus which did not completely fill the lumen was attached at this denuded point. The section taken from the anterior descending branch presented a similar picture, except that there was no thrombus. The adjoining myocardium revealed no marked changes from normal.

The nodules taken from the left lung were found to have caseous centers surrounded by cellular reactions typical of tuberculosis. No similar lesions were encountered grossly or microscopically in any other organ. The liver showed slight congestion of the blood sinusoids and fatty infiltration.

CASE 8.—On the morning of June 13, 1944, a 27-year-old sergeant was undergoing a test of physical fitness with his company. While on a hike following violent exercise the soldier fell. He was taken immediately to the hospital and upon arrival was found to be dead. There had been no hospital admission previously, and the patient had had a physical examination several weeks previously which revealed no disease. However, the soldier had in his pocket on arrival at the hospital a partly used package of "crush ampules of ammonia" which suggested that he may have had some cardiac symptoms.

Autopsy Findings.—The heart weighed 357 grams and all chambers were filled with partially clotted blood. No areas of scarring or infarction were seen. Just below the origin of the anterior descending branch of the left coronary artery there was a soft symmetrical plaque which reduced

the lumen to about one-third of normal. Below this, in several areas, the walls of the vessel were calcified, but very little thickening was evident. In the circumflex branch of the left coronary artery there were several small soft plaques. Near the origin of the right coronary artery there was a large irregular plaque surrounding the lumen and reducing its caliber.

The intima of the thoracic aorta was flecked with yellowish streaks and spots. The lungs were crepitant in consistency, and only a small amount of dark blood oozed from the cut surface. The liver weighed 2,214 grams, and dark blood oozed freely from the cut surface.

Microscopic sections of the myocardium were normal. Sections taken from the coronary arteries showed marked atherosclerosis with varying degrees of fibrosis and calcification. Sections of the aorta revealed slight irregular lipoidal infiltration of the intima.

Lung sections showed only congestion of the interalveolar capillaries. Sections of the liver showed congestion of the blood sinusoids and fatty infiltration.

CASE 9.—Little history could be obtained on a 39-year-old soldier who, for several days prior to admission, had complained of vague abdominal distress. Shortly before death he was lying on his bed because of abdominal distress. He arose, gasping for breath, and expired suddenly.

Autopsy Findings.—The heart weighed 345 grams. There were no gross abnormalitics of the myocardium. The left main coronary artery showed marked thickening and narrowing of the lumen about 1.0 cm. proximal to its bifurcation; the sclerotic process extended along the anterior descending branch throughout its length. The circumflex branch of the left coronary artery for a distance of about 3.0 cm. showed a similar sclerotic process. Numerous plaques were also seen in the right coronary artery.

The aorta revealed atherosclerosis of varying degrees. In the abdominal portion there were numerous thick plaques from which the covering aortic intima seemed to be absent.

The pulmonary arteries showed numerous, irregular, yellowish plaques projecting into the lumina of the vessels. A firm calcified node about 1 cm. in diameter was found in the upper lobe of the left lung. There was no scarring, and the lungs were crepitant. The liver weighed 1,700 grams and was firm in consistency. The brain revealed no cephalomalacia or other abnormality, although the posterior communicating arteries showed numerous intimal plaques which produced no marked narrowing of the vessels.

Microscopic examination of the myocardium revealed a rather diffuse interstitial fibrosis and degenerative changes of the muscle fibers. Sections of the coronary vessels revealed sclerosis which resulted in narrowing of the lumina of the vessels. The aorta showed sclerosis of varying degree with scarring of the media.

The lungs showed numerous mononuclear, pigment-filled cells in the alveoli. A fresh thrombus was seen in one of the smaller pulmonary radicles. The liver cells were well preserved although the blood sinusoids and central veins were moderately congested. Multiple sections of the brain revealed no abnormality.

DISCUSSION

The clinical features of the cases are summarized in Table I.

French and Dock* have called attention to certain clinical features of coronary artery disease in young soldiers. Seventy-three of their eighty patients showed some degree of obesity. In none of the cases which we have reported was obesity mentioned in the autopsy protocols. The estimated weights and actual measurements tabulated in Table I indicate that only one patient (Case 3)

*French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. 124: 1233, 1944.

TABLE I. SUMMARY OF CLINICAL FEATURES IN NINE CASES OF FATAL CORONARY DISEASE

CASE	HEIGHT (INCHES)	WEIGHT (POUNDS) (ESTIMATED)	AGE (YEARS)	SYMPTOMS	ACTIVITY IMMEDIATELY PRECEDING DEATH
1	61	115	22	None	Marching
2	65	135	33	None	Violent exertion
3	69	200	31	None	Lying in bed
4	68	165	27	None	Drunkenness
5	66	160	27	None	Drilling
6	67	145	34	None	Lying in bed
7	67	145	38	Mild dyspnea	Getting up and eating breakfast
8	69	160	27	(?) Relieved by ammonia	Violent exertion
9	68	Well developed and nourished	39	Abdominal distress	Lying in bed

could be considered as markedly obese. It is of interest to note that none of the men was above average height, and there was a tendency in the series toward shortness of stature. This was most marked in the patient in Case 1.

French and Dock failed to find any racial predominance among their cases. All of the nine patients reported on by us had English, Scotch, or Irish names, except one (Case 7). There were no Negroes in the series.

As for precipitating influences, it can be seen that in three instances death occurred while the subjects were at rest; it cannot be stated definitely in every case that the soldiers were not resting because of some symptom. In two cases death occurred immediately after violent exercise; in two, during moderate exercise (marching and drilling); in one, during or after an alcoholic debauch; and in one death occurred on beginning the morning activity.

In only three of the nine cases (Cases 7, 8, and 9) did the records give any indication of even slight symptoms of coronary artery disease before sudden death. It is striking that symptoms were so few and so mild and that not one patient lived to reach the hospital. It is a matter for conjecture whether a thorough medical history taken before the death of the nine soldiers would have revealed symptoms of chest or epigastric discomfort or dyspnea. If such symptoms had been elicited, it is quite possible that they would have been thought inconsequential. I have been impressed by the relative frequency of mild chest or epigastric discomfort of vague character complained of by soldiers in a separation center.

TABLE II. SUMMARY OF PATHOLOGIC FEATURES IN NINE CASES OF FATAL CORONARY DISEASE

CASE	HEART WEIGHT (GRAMS)	LIVER WEIGHT (GRAMS)	CORONARY ARTERIES	MYOCARDIUM	INCIDENTAL FINDINGS
1	280	1,596	Atherosclerosis of anterior descending and right marginal	Cloudy swelling	None
2	308	2,156	All of main branches of coronary arteries sclerotic, with calcification	Fibrosis; degeneration; cellular infiltration	None
3	475	2,320	Marked atherosclerosis of left coronary and its branches	Degeneration; neutrophilic and mononuclear infiltration	None
4	364	2,170	Atherosclerosis of left and right coronary arteries; calcification	Patchy fibrosis; fragmentation of muscle cells; cellular infiltration	Patent ductus arteriosus; small hemangioma of liver
5	460	1,500*	Atherosclerosis, generalized; recanalized thrombus in left circumflex	Fibrosis; hyalinization and cellular infiltration; degeneration	None
6	392	1,757	All of main branches of coronaries sclerotic, most marked in branches of left; fresh thrombus of anterior descending; occlusion of right marginal	Fibrosis; degeneration and cellular infiltration; hyalinization	None
7	364	2,100	Atherosclerosis of left coronary and its branches; fresh thrombosis of left main coronary	No abnormality	Tuberculous focus
8	357	2,214	Sclerosis of main right coronary and branches of left; calcification	No abnormality	None
9	345	1,700	Generalized sclerosis	Fibrosis; degenerative changes; interstitial fatty infiltration	Thrombosis of one of pulmonary artery radicles

*Estimated.

In considering certain pathologic factors, it should be emphasized that there was no valvular heart disease or other pathologic findings which could be considered as even a contributory cause of death.

The pathologic data are summarized in Table II. It should be remembered that the term *infarct* is purposely not used because its use may give the impression that fresh areas of necrosis were seen. In no case was a fresh area of necrosis observed, although all but three of the hearts showed evidence of old infarction.

It can be seen that only two of the hearts (Cases 3 and 5) weighed over 400 grams, although seven of the nine myocardia showed evidence of insult. This is in agreement with the opinion of French and Dock that cardiac hypertrophy is not a marked feature of coronary artery disease in young persons.

In most of the nine cases, the liver showed a moderate degree of enlargement; the weight averaged 1,946 grams. It cannot be stated definitely that this enlargement was secondary to the cardiovascular condition.

The coronary arteries showed all degrees of atherosclerosis. Many contained areas of calcification, hyalinization, cholesterol deposits, and fibrous replacement of the media. In three of the nine cases, thrombosis of one of the coronary arteries was present. Thrombosis occurred in the anterior descending branch of the left coronary artery in one patient, in the main left coronary artery in one, and in the circumflex branch of the left coronary in one patient.

The state of the coronary circulation did not always accurately reflect the state of the myocardium. There were varying degrees of scarring, fibrosis, and cellular infiltration in the myocardia, but in none of the hearts was there seen a fresh, completely necrotic area infiltrated by neutrophiles and surrounded by interstitial hemorrhage. Perhaps no fresh infarction had had time to develop since all of the deaths were sudden.

Incidental findings are recorded as a matter of record in Table II and are not emphasized in the case reports for their recounting would be irrelevant.

SUMMARY

1. A detailed report of nine cases of fatal coronary artery disease in men between the ages of 22 and 40 years is made.

2. These nine cases comprised 3.2 per cent of all autopsies, a total of 280, performed on men between 18 and 40 years of age.

3. The nine cases comprised 7.4 per cent of all autopsies, a total of 121, performed on men between the ages of 18 and 40 years who died of natural causes.

4. Very few of these nine young men gave evidence of having had symptoms of coronary disease before the fatal episode.

5. Death was sudden and unheralded.

6. Most of the nine young men who died of coronary artery disease were of average or below average height.

7. Cardiac weight did not reflect the seriousness of the cardiac condition. Slight to moderate enlargement of the liver may have been related to the cardiac disease.

8. Evidence of old myocardial injury is frequent; evidence of fresh infarction is rare in young men dying of coronary artery disease.

THE EFFECT OF SULFONAMIDE ADMINISTRATION ON CARDIAC FUNCTION IN THE DOG

ROBERTA HAFKESBRING, PH.D., AND GRACE E. WERTENBERGER, PH.D.
PHILADELPHIA, PA.

SEVERAL reports on the histopathologic effects of the sulfonamides upon cardiac muscle have appeared in the literature, but very few have dealt with the physiologic effects, in spite of the extensive clinical use of these compounds.

While the kidney and liver were frequently the site of histopathologic changes in the experimental studies on toxicity, only a few reports showed cardiac involvement. Nelson[1] examined the tissues in a large series of rabbits and hens which were given fatal doses of sulfanilamide. In twenty-six rabbit hearts examined, twenty-five were normal although other organs showed marked changes, while in seventeen hen hearts, twelve were normal and five showed some slight myocardial change. Maisel, McSwain, and Glenn[2] studied the effects of sulfadiazine on dogs and found histologic changes in the myocardium in only three of the fourteen treated animals. In man, French and Weller,[3] in a critical survey of the necropsy findings in 238 patients who were given sulfonamide therapy shortly before death, reported 126 instances of interstitial myocarditis "rich in eosinophil cells." No correlation could be made between the duration and intensity of therapy with the extent of the myocardial lesions. They succeeded in producing a similar lesion in thirty-eight of sixty mice and thirty-three of forty-seven rats given daily intraperitoneal injections of various sulfonamides in amounts slightly less than the usual clinical dose. In this series, the frequency of the lesion increased with the duration of the treatment. Lederer and Rosenblatt[4] reported four cases of "sulfathiazole death" in which two cases showed "areas of focal necrosis" in the myocardium. Rich[5] reported on a patient in whom sulfathiazole was administered as a prophylactic measure before operation for squamous-cell carcinoma. Widespread fresh lesions of periarteritis nodosa were found at autopsy in the heart and other viscera on microscopic examination, although no significant lesions were noted macroscopically. In addition to these vascular lesions, there was a "diffuse inflammatory infiltration of the myocardium" closely resembling that described by French and Weller[3] in their patients treated with sulfonamides. This case presents further support for Rich's previous suggestion[6] that vascular lesions of the periarteritis nodosa type are the

From the Department of Physiology, Woman's Medical College of Pennsylvania.
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result of an anaphylactic type of hypersensitivity reaction to some sensitizing antigen—in this case, the sulfonamides.

Attention was first directed toward possible functional cardiac effects during sulfonamide therapy in man by Dozzi[7] who reported the occurrence of "transient nodal rhythm" in a 27-year-old physician, who was subject to occasional attacks of paroxysmal tachycardia, following a single massive dose of sulfanilamide for a throat infection. An electrocardiogram was taken when the patient complained of cardiac irregularity and this showed a rapid A-V nodal rhythm. Scheinberg and Ingle[8] reported a case "suggestive of myocardial sulfanilamide myocardosis" since the electrocardiogram showed prolongation of both P-R and QRS intervals with left ventricular predominance. The absence of electrocardiograms taken before and after chemotherapy for comparison makes it difficult to evaluate these findings. Frist,[9] in analyzing the effects of sulfonamides in 186 patients, reported "cardiac involvement" in two patients given sulfathiazole. Only one case was described and the electrocardiogram showed bundle branch block. The case history revealed that the patient had been given five courses of "sulfonamide compounds" in a period of nine months with severe toxic reactions with each course. After the third course, he complained of fatigue and dyspnea on exertion, and after the fifth course, increased dyspnea, abdominal swelling, ankle edema, and increased weight. Four months later he was hospitalized because of frank heart failure and because the electrocardiogram revealed bundle branch block. At autopsy the heart showed "myocardial hypertrophy with degeneration, fibrosis of anterior wall of each ventricle and of the septum, and extensive mural thrombosis." Micropscopic examination showed infiltration and proliferative changes in the myocardium.

Other evidence of functional involvement, but not accompanied by electrocardiographic findings, have appeared in several reports. Hoyne and Larimore[10] reported heart sounds "that were distant and of poor quality though no murmurs were present" after prolonged sulfathiazole therapy in a previously healthy man who had acute agranulocytosis. "Distinctive cloudy swelling of the myocardium" was found at autopsy. Browne, Marvin, and Smith[11] reported transient sinus bradycardia (under 60 beats per minute) in 63 of 100 consecutive cases of pneumonia in which the patients were treated with sulfadiazine. This bradycardia developed two to four days after the return to normal temperature and lasted one to four days. In seven cases the heart rate was below 40. Wells and Sax[12] reported "heart sounds that were distant and of poor quality but no murmurs" in a patient who died suddenly following ten days of sulfadiazine therapy. Histologic changes typical of a "diffuse form of isolated myocarditis" were found at autopsy.

Morphologic changes in the heart, of the magnitude reported in these studies, might well be expected to produce functional changes which would be reflected in the electrocardiogram. Although cardiac involvement is not a constant finding during sulfonamide administration, its incidence is frequent enough to warrant investigation. This study was therefore organized to investigate the effects of various sulfonamides, given in doses comparable to those used clinically, upon

cardiac function as revealed by the electrocardiogram. In the first part of the study, presented in a preliminary report,[13] the sulfonamides used produced no permanent effect on the electrocardiogram, although two dogs showed a transient effect; namely, occasional premature systoles during treatment. Rate changes varied.

PROCEDURE

Mongrel female dogs whose body weight averaged 8 kilograms were used. The animals were carefully selected and in excellent condition during the control period before starting medication.

The drugs studied were sodium sulfathiazole, sodium sulfadiazine, sodium sulfapyridine, sodium sulfamerazine, and sodium sulfapyrazine. In order to insure a maximal effect of the drug, the method described in the previous report was altered somewhat by lengthening the period of drug administration. No twenty-four hour experiments were made in this series.

The drugs were administered by intraperitoneal injection in courses of four doses each, given daily; a rest period of at least one week was allowed after each course.

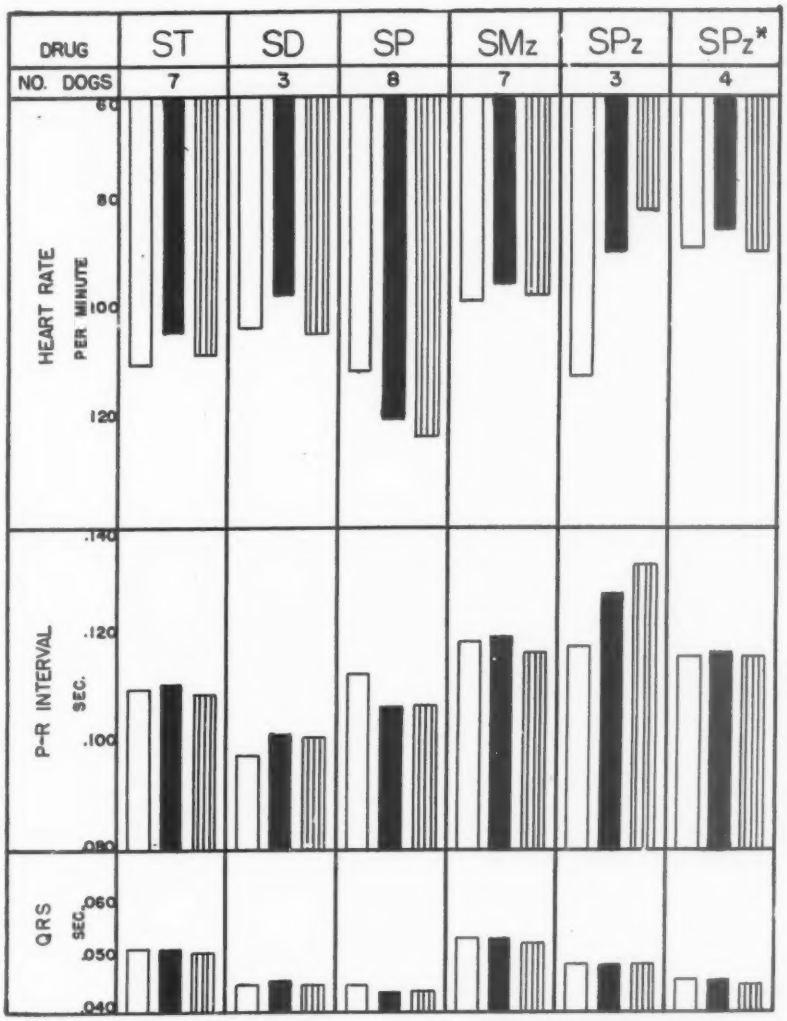
A standard dose was used throughout, a total of 0.65 Gm. per kilogram of body weight for each course of treatment: 0.2 Gm. per kilogram as the initial dose and 0.15 Gm. per kilogram thereafter. This method was chosen rather than attempting to keep a standard blood level because of the wide variation in absorption and excretion in individual animals. While this insured a therapeutic level, in some cases in which the more slowly excreted sulfonamides were used, the level rose well above the therapeutic standard (Table I). This was especially true of sodium sulfapyrazine in which the slow excretion rate resulted in blood levels that caused such a high mortality rate that a lighter dose had to be chosen in order to carry the animals through the entire four courses of treatment (Table II). The total dose was therefore lowered to 0.45 Gm. per kilogram, given in divided doses over four days.

The unanesthetized dogs were trained to lie quietly on their left side while the electrocardiogram (Lead II) was taken. This position was maintained routinely throughout the study. A Hindle No. 3 electrocardiograph was used.

From eight to sixteen control tracings were taken on each animal during the two-week preliminary observation period. During medication two tracings were taken daily, one in the morning just before injection and the second three and one-half to four hours after injection. The blood sample for drug determination was usually drawn immediately after the second tracing. Three to five electrocardiograms were taken at intervals during the rest periods between drug courses and after the fourth course until the drug had disappeared from the blood.

The tracings were analyzed for rate, abnormalities in rhythm, P-R interval, QRS and T waves, and position of S-T segment. Any deviation from the normal electrocardiogram was carefully recorded. The average values obtained from each dog's control tracings were used as a basis for the comparison of effects of medication in that animal.

Since this detailed analysis of the electrocardiograms of Series I was not included in our preliminary report,[13] this has been summarized with the analysis of Series II and is included in Table I and Fig. 1 of this paper.



*Refers to dogs given light dose.

Fig. 1.—Summary of electrocardiographic findings on dogs given various sulfonamides which survived two or more courses of the drug. Correlation of rate and P-R and QRS intervals during control period, white columns; drug administration, solid columns; and recovery, striped columns.

RESULTS

Control Electrocardiograms.—In the dogs having a "normal" electrocardiogram, the heart rate ranged from 62 to 141 per minute; the P-R interval, from 0.134 to 0.091 second; and the QRS duration, from 0.059 to 0.026 second.

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN DOGS GIVEN CERTAIN SULFONAMIDES (ANALYSIS OF LEAD II IN THIRTY-NINE DOGS)

DRUG	DOG	DOSES	CONTROL					DURING MEDICATION					AFTER MEDICATION				SUMMARY
			RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T_2 WAVES	OTHER ECG CHARACTERISTICS	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	BLOOD LEVEL (MG. %)	EFFECT ON ECG	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T_2 WAVES	
Sodium sulfamerazine	12	16	100	.097	.052	T −	S-T negative	122	.092	.050	33.0	Rate rise only change	111	.095	.052	T −	No change from control ECG
	15	16	93	.109	.056	T±	S-T negative; marked sinus arrhythmia	104	.105	.056	41.0	Rate rise only change	114	.102	.056	T±	Rate increase only change in ECG
	16	16	98	.114	.058	T −	S-T markedly depressed; prolonged P-R	83	.131	.059	37.0	P-R frequently increased (.152; .144); rate fell	101	.124	.058	T −	Prolonged conduction time only change from control ECG
	20	16	92	.122	.045	T+	"Normal"	79	.129	.046	25.0	Rate fall only change	89	.120	.044	T+	No change from control ECG
	21	16	100	.131	.052	T −	Prolonged P-R interval with A-V block	81	.127	.050	33.6	Rate fall only change	81	.127	.050	T −	Rate decrease only change in ECG; degree of A-V block unaffected by drug
	22	16	100	.119	.061	T+	Slurred S	89	.119	.061	32.6	Elevated S-T segment T±; T −	92	.116	.059	T+	T and S-T segment changes disappear
	23	16	103	.138	.051	T −	Deep S; prolonged P-R interval with A-V block	107	.135	.051	25.0	Slight rate rise only change	90	.137	.050	T −	Rate decrease only change in ECG; degree of A-V block unaffected by drug
Sodium sulfapyrazine	14	16	113	.119	.044	T±	"Normal"	91	.125	.044	86.6	T wave +; marked rate decrease	84	.130	.044	T±	Marked rate decrease only change in ECG
	10	12	116	.115	.051	T+; T±	"Normal"	90	.124	.051	57.5	Marked rate decrease only change	78	.130	.051	T+; T±	Marked rate decrease only change in ECG

Sodium sulfapyrazine —Cont'd	8	8	106	.121	.052	T −; ±; +	Prolonged P-R interval	86	.135	.052	80.0	Marked rate decrease only change	81	.138	.052	T −; ±; +	Marked rate decrease only change in ECG
	9	8	112	.132	.052	T+	Prolonged P-R interval	106	.124	.052	84.7	Rate decrease, S-T segment depressed and T± after Dose 5 until death	104	.120	.052	T±	Rate fell; S-T segment depressed and T diphasic up to time of death
	17	4	101	.127	.048	T+	"Normal"	83	.125	.051	70.0	Marked rate decrease only change	98	.124	.049	T+	No change from control ECG despite severe drug reaction
	18	4	135	.103	.047	T+	"Normal"	83	.119	.046	69.0	Marked rate decrease only change	59	.134	.045	T+	Marked rate decrease only change in ECG; dog died
	19	4	129	.114	.054	T −	"Normal"	104	.134	.053	88.0	Marked rate decrease only change	—	—	—	T −	Marked rate decrease only change in ECG; dog died
	24*	16	84	.111	.043	T+	"Normal"	84	.114	.044	41.8	S-T segment depressed; T −; P-R interval increased	83	.114	.044	T+	Prolonged P-R interval persists though S-T segment and T waves return to normal
	25*	16	97	.108	.042	T+	"Normal"	93	.109	.042	44.5	S-T segment depressed and T± in most tracings	99	.109	.041	T±	Depression of S-T segment and diphasic T waves persist
	26*	16	88	.115	.039	T+	"Normal"	88	.111	.038	52.5	No change	93	.109	.037	T+	No change from control ECG
	27*	16	83	.128	.059	T+	"Normal"	76	.134	.059	46.0	Slight rate decrease only change	81	.131	.059	T+	No change from control ECG
Sodium sulfathiazole	2	16	141	.097	.045	T −	"Normal"	130	.101	.044	16.6	Rate fall only change	125	.101	.044	T −	Rate decrease only change in ECG
	7	12	111	.106	.059	T −	S-T segment negative	109	.105	.059	9.0	No change	108	.106	.058	T −	No change from control ECG
	1a	14	62	.134	.044	T±	"Normal"	75	.130	.044	—	Rate rise only change	79	.126	.044	T±	Rate increase only change in ECG
	2a	14	133	.108	.036	T±	S-T segment negative; marked sinus arrhythmia	122	.196	.036	—	Rate fall only change	120	.106	.036	T±	Rate decrease only change in ECG

*Light dose. See Table II.

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN DOGS GIVEN CERTAIN SULFONAMIDES (ANALYSIS OF LEAD II IN THIRTY-NINE DOGS)—CONT'D

DRUG	DOG	DOSES	CONTROL					DURING MEDICATION					AFTER MEDICATION				SUMMARY
			RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T_2 WAVES	OTHER ECG CHARACTERISTICS	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	BLOOD LEVEL (MG. %)	EFFECT ON ECG	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T_2 WAVES	
Sodium sulfathiazole —Cont'd	3a	11	92	.116	.045	T±	S-T segment negative	73	.120	.044	——	Marked rate fall only change	83	.122	.044	T±	Rate decrease only change in ECG
	4a	8	110	.106	.028	T−	"Normal"; very short QRS	100	.104	.029	——	Rate decrease only change	98	.101	.028	T−	Rate decrease only change in ECG
	5a	8	123	.106	.027	T−	"Normal"; very short QRS	121	.109	.028	——	No change	142*	.102	.027	T−	Rate increase after drug only change in ECG*
Sodium sulfadiazine	1	16	103	.104	.045	T±	S-T segment negative	100	.108	.049	72.0	No change	102	.108	.045	T±	No change from control ECG
	3	16	108	.091	.044	T−	"Normal"	95	.099	.045	60.0	Marked rate decrease only change	101	.097	.045	T−	No change from control ECG
	4	16	99	.099	.045	T−	"Normal"	95	.099	.045	45.5	No change	108	.098	.045	T−	No change from control ECG
	6a	10	77	.123	.035	T+	"Normal"	80	.119	.035	——	No change	79	.127	.037	T+	No change from control ECG though dog died after Dose 10 during Course 2
	7a	5	89	.120	.038	T−	"Normal"	92	.121	.038	——	No change	131	.106	.037	T−	Marked rate increase, dog very ill; died 6 days after Dose 5; no change in ECG complex
	8a	4	108	.110	.036	T−	"Normal"	113	.099	.036	——	No change	98	.110	.036	T−	No change from control ECG

Sodium sulfa-pyridine	10a	17	102	.131	.039	T −; ±; +	"Normal"	108	.126	.038	——	Slight rate increase	109	.124	.038	T −; ±; +	No change from control ECG
	11a	17	85	.128	.040	T −	"Normal"	106	.119	.040	——	Rate rise only change	99	.120	.040	T −	Rate rise only change in ECG
	5	16	125	.094	.037	T ±	S-T negative	130	.090	.036	8.8	Slight rate increase	125	.090	.036	T ±	No change from control ECG
	6	16	113	.110	.052	T+; T ±	"Normal"	130	.096	.052	10.0	Rate rise only change	125	.098	.052	T+; T ±	Marked rate increase only change in ECG
	12a	10	124	.117	.034	T −	"Normal"	157	.100	.034	——	Rate rise only change	165	.098	.034	T −	Marked rate increase only change in ECG
	13a	8	132	.104	.042	T −; T+	"Normal"	108	.108	.042	——	Rate fell; S-T depressed and T − in some cases	119	.109	.041	T −; T+	Rate decrease; S-T segment and T waves return to control
	14a	8	98	.112	.037	T −	"Normal"	97	.109	.037	——	S-T segment depressed in some cases	108	.106	.035	T −	S-T and T wave return to "normal"; rate rise only change
	15a	11	110	.108	.026	T+; ±; −	"Normal"; very short QRS	121	.108	.026	——	Rate rise	119	.107	.026	T+; ±; −	Rate rise only change in ECG

*Average of only two tracings.

TABLE II. MILLIGRAMS PER CENT OF FREE SODIUM SULFAPYRAZINE IN BLOOD OF DOGS AT TWO DOSE LEVELS

LIGHT DOSE (0.45 GM./KG./COURSE)					HEAVY DOSE (0.65 GM./KG./COURSE)							
DOG	24	25	26	27	DOG	14	10	8	9	17	18	19
Control	0.8	0.7	0.7	0.7	Control	1.5	0.5	0.4	0.4	0.4	0.3	0.5
After Dose 4	52.9	53.9	56.3	51.9	After Dose 4	67.4	38.1	64.8	58.1	70.3	75.0	89.1
Ten days after Dose 4	3.6	4.2	1.9	2.5	Before Dose 5	9.9	1.4	15.1	25.3	Died eight days later; blood level, 37.9	Died seven days later; blood level, 40.2	Died one day later
After Dose 8	47.1	43.4	41.7	49.6	After Dose 8	80.7	85.7	95.2	111.4			
Eleven days after Dose 8	0.8	0.8	1.0	2.8	Four days after Dose 8	—	49.6	64.1	83.0 (Died)			
After Dose 12	35.9	28.5	47.9	31.1	Twenty-five days after Dose 8	31.1	0.5	3.1 (Sick)				
Eleven days after Dose 12	0.5	0.8	1.2	1.1	After Dose 12	—	48.9 (Sick)	Dogs so ill drug discontinued				
After Dose 16	30.6	52.0	64.4	51.6	After Dose 16	111.7						
Eleven days after Dose 16	0.5	7.1	1.2	1.2	Eighteen days after Dose 16	42.9						

Fourteen of the thirty-nine animals showed abnormalities in their control electrocardiograms such as pronounced sinus arrhythmias (two); prolonged conduction time (five); A-V block (two); S-T segment deviation (nine); and slurred S waves (two). T waves were variable. The appearance of negative T waves in Lead II is a common occurrence in the dog electrocardiogram and is not considered of pathologic significance. The rate ranged from 92 to 133; the P-R interval, from 0.094 to 0.138 second; and the QRS duration from .061 to .036 second.

Sulfathiazole.—In the seven dogs given sulfathiazole, three of which showed depression of the S-T segment in their controls, no change occurred in the electrocardiogram during or after medication. While four dogs showed a fall in rate, the marked increase in Dog 5a after drug administration is misleading (Table I) since this is an average of only two tracings.

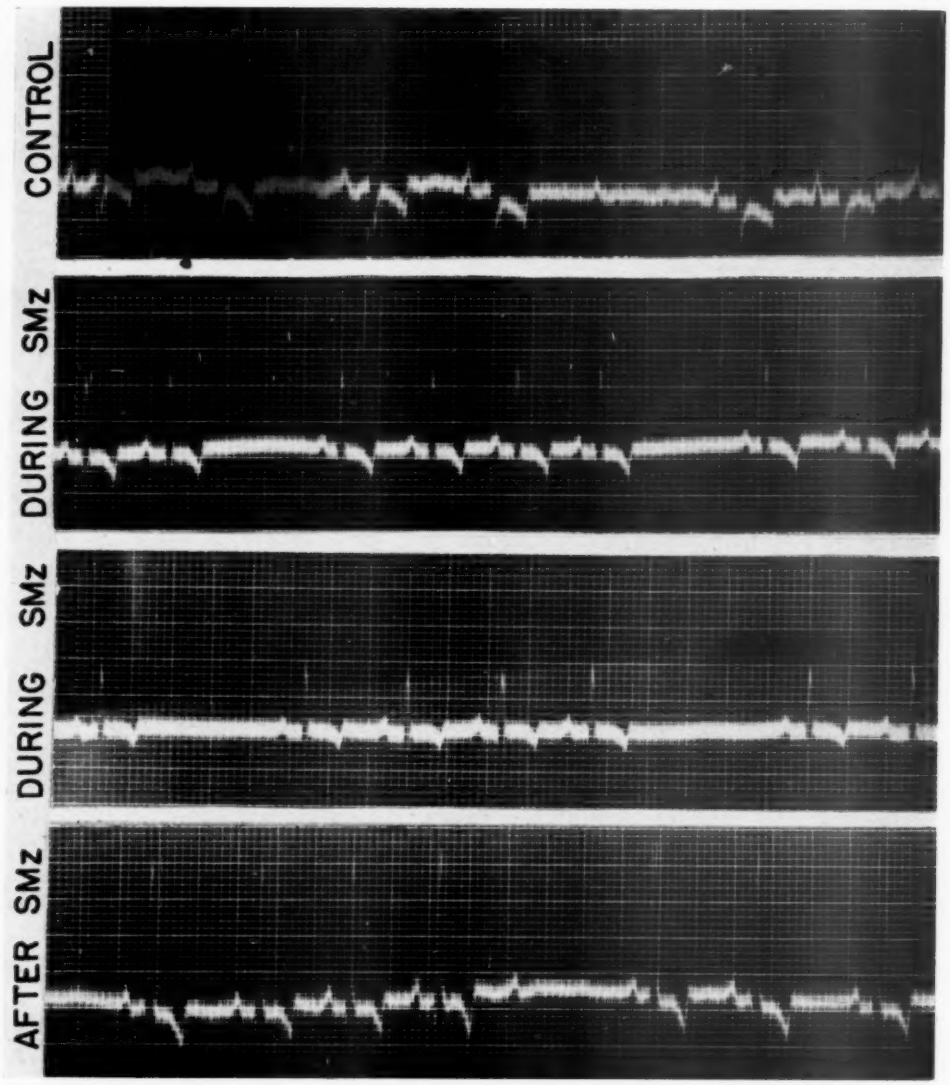
Sulfadiazine.—In the six dogs given sulfadiazine, only one of which showed depression of the S-T segment in the controls, no change occurred in the electrocardiogram following drug administration. This is especially significant since Dogs 6a and 7a (Fig. 4) died after Doses 10 and 5, respectively. Both dogs were very ill and lost weight during medication.

Sulfapyridine.—Of the eight dogs to which sulfapyridine was given, only one of which showed depression of the S-T segment, transient electrocardiographic changes in the form of depression of the S-T segment and inversion of the T wave occurred during medication in Dogs 13a and 14a. These changes disappeared after stopping the drug. An increased rate occurred in seven dogs.

Sulfamerazine.—Of the seven dogs given sulfamerazine, only one had a "normal" control electrocardiogram. Three dogs showed depression of the S-T segment, three showed prolonged P-R intervals, and two of these, Dogs 21 and 23 (Fig. 2), showed A-V block, while Dog 22 had a long QRS complex with slurring of the S waves. This group of animals showing definite cardiac abnormality seems especially interesting since the excretion rate of sulfamerazine is so slow that a consistently high blood level can be maintained during medication. Every dog showed an average blood drug level above 25 mg. per cent during each course of the drug and Dog 15 averaged 41 mg. per cent (Table I). All animals showed some toxic effects during medication including nausea, vomiting, and anorexia.

In spite of the evidence of toxicity, no permanent changes occurred in the electrocardiogram. The degree of block shown by Dog 21 during the control period was not increased by sulfamerazine, and dropped beats occurred (Fig. 2) throughout the experiment. Dog 23 (Fig. 2), whose control showed a greater degree of A-V block since dropped beats occurred in a 5:4 and 4:3 ratio, showed no change with the drug. Wenckebach periods (0.132, 0.136, 0.156, 0.160 second) were present throughout. Dog 22, however, whose control electrocardiogram showed a slurred S wave with a relatively long QRS complex, showed elevation of the S-T segment and a change in the direction of the T wave on some days during medication. These changes disappeared after the drug was stopped.

Sulfapyrazine.—Of the eleven dogs to which sulfapyrazine was given, two showed prolonged P-R intervals, while the others had "normal" control electrocardiograms.



A.

Fig. 2.—Effect of sulfamerazine. *A*, Three tracings of Lead II from Dog 21 who had conduction defects, prolonged P-R intervals, and A-V block. Four courses of the drug did not affect the degree of block and no change occurred in the electrocardiogram.

B, Three tracings of Lead II from Dog 23 who had pronounced block showing Wenckebach periods (0.112 second, .128 second, and .136 second) in the control. The degree of block was unaffected by four courses of the drug and no change occurred in the electrocardiogram.

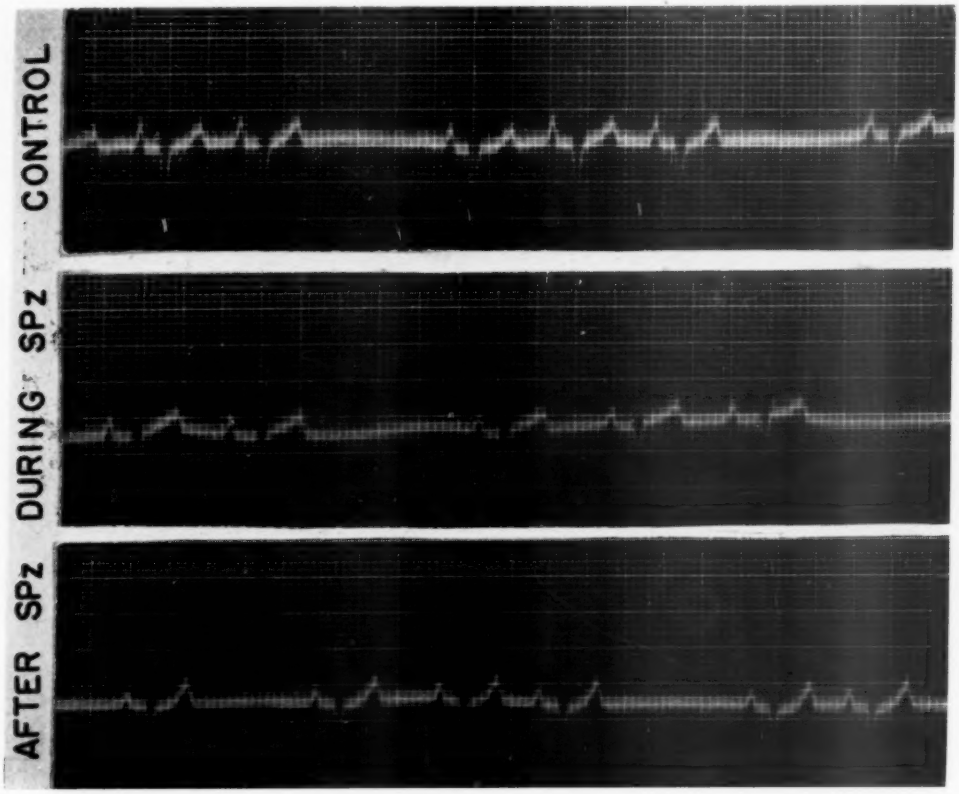
The drug, in the 0.2 Gm. dose, was so slowly excreted and proved so toxic that four of the seven dogs died after the first course, and the drug had to be discontinued after Course 2 and after Course 3 in Dogs 8 and 12. Only one, Dog 14, survived the full course of sixteen doses. Because of this high mortality, the smaller dose was used on the remaining four dogs. Drug elimination in these two groups is shown in Table II.

B.

Fig. 2. —*(For complete legend see opposite page.)*

In the group on heavy dosage, Dogs 14 and 9 showed electrocardiographic changes during medication. Dog 9 died five days after Dose 8, with a drug blood level of 83 mg. per cent twelve hours before death. Its control electrocardiogram showed a prolonged conduction time (.132 second; rate, 112 per minute) which was not affected by the drug, but the S-T segment was depressed and the T wave became diphasic. These changes did not appear until after Dose 5 in the second course, when the blood drug level had started to rise (111 mg. per cent after Dose 8) and persisted until death (Fig. 3, *B*). Drug elimination was slow.

Dog 14, which survived the full sixteen doses of the drug, had a diphasic T wave in the control. This became positive and increased in amplitude during drug administration but returned to the control pattern after the drug was withdrawn. Drug elimination was so slow that the blood level did not return to normal during the rest periods. Thus the drug accumulated in the blood with each new course and after Dose 16 reached the very high level of 112 mg. per cent. It was still 48 mg. per cent at the end of the usual ten-day observation



A.

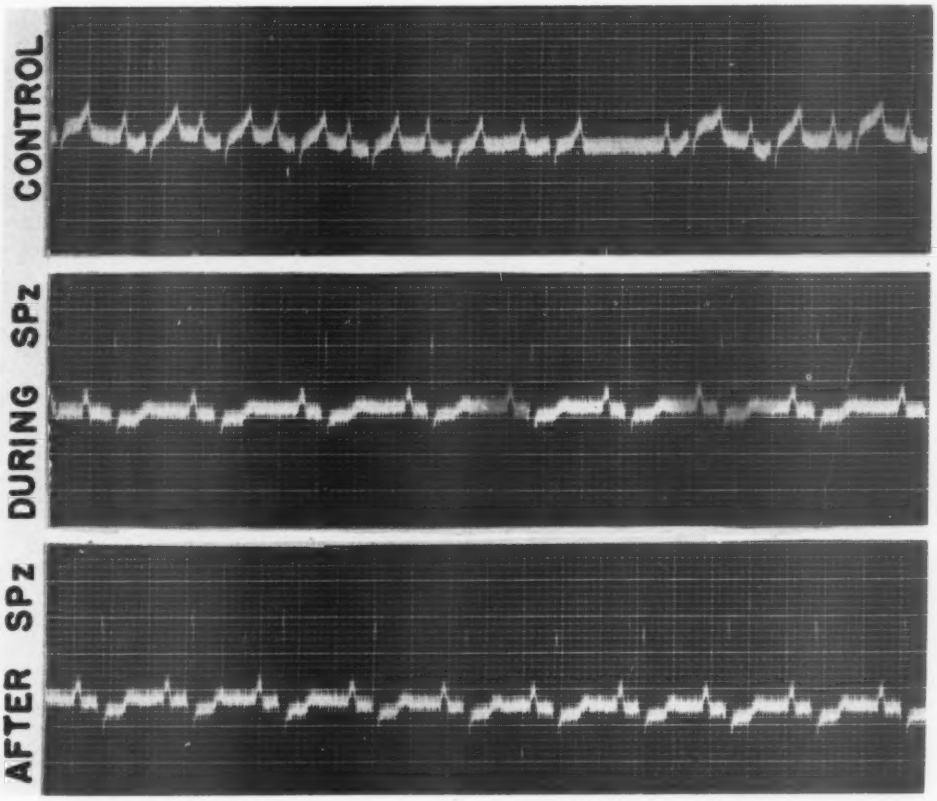
Fig. 3.—Effect of sulfapyrazine. *A*, Three tracings of Lead II from Dog 27 with a "normal" electrocardiogram showing the sinus arrhythmia often found in the dog. Four courses of sulfapyrazine had no effect on the electrocardiogram and the rhythmicity was unchanged.

B, Three tracings of Lead II from Dog 9. After two courses of sulfapyrazine, the S-T segment shifted downward. This change persisted throughout the remainder of the experiment.

period and 43 mg. per cent eight days later, at which time the heart rate was 56. In spite of the persistence of the high blood level, the electrocardiogram had returned to "normal." The remaining five dogs on heavy dosage showed no electrocardiographic changes, although the toxic effects of the drug were so severe that three died during drug administration and in two instances the drug

was discontinued before completing the full course of sixteen doses (Table II). A marked depression of rate occurred in all dogs during drug administration which persisted after medication.

There were no abnormalities in the control electrocardiograms of the four dogs on the lighter dose. Dog 24 showed a transient depression of the S-T segment and a change in direction of the T wave during medication. In some of



B.

Fig. 3.—*(For complete legend see opposite page.)*

these tracings, there seemed to be a slight increase in conduction time which was also present after the drug was withdrawn. Dog 25 also showed S-T segment depression and a diphasic T wave in most tracings during drug administration; both of these electrocardiographic changes persisted. No changes occurred in the other dogs throughout the experiment (Fig. 3, *A*). No significant rate changes occurred in any of this group. The lighter dose was well eliminated during the rest periods and the drug was gone from the blood before the next course was begun (Table II), thus preventing cumulative effects during the experiment.

Some toxic effects were present, however, during drug administration, and the animals showed a slight weight loss due to vomiting and anorexia while the blood level was high.

DISCUSSION

The high incidence of deviation from the "normal" electrocardiogram in these apparently healthy dogs emphasizes the need for well-established control observations on dogs, especially in any study involving the cardiovascular system, in order to avoid the danger of erroneously attributing such changes to the experiment. A recent study by Morehead and Little[14] further emphasized this need. They reported blood vessel changes in twenty-eight "healthy" mongrel dogs showing a high incidence of extensive vascular changes in all age groups, even puppies. Thirty-five per cent of our animals, which were carefully chosen to be in a young adult group and healthy as far as physical examination could determine, showed abnormalities in conduction.

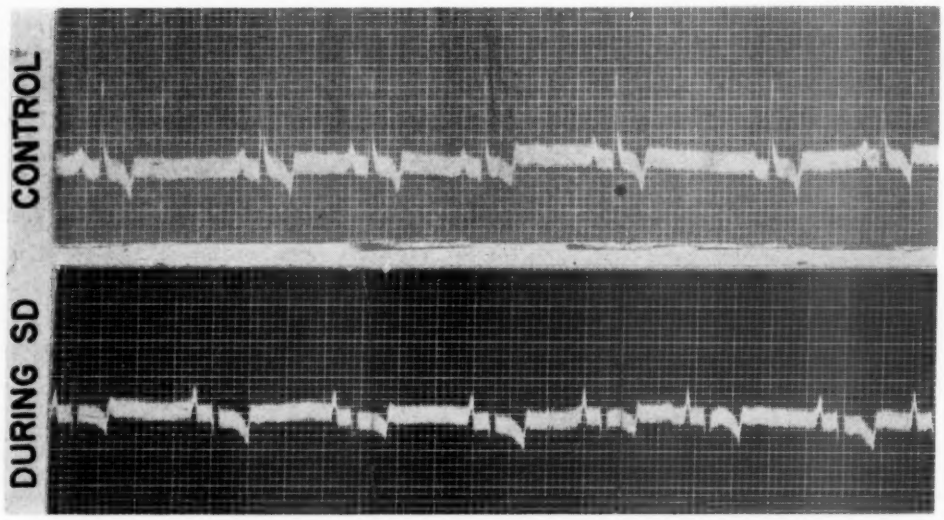


Fig. 4.—Effect of sulfadiazine. Two tracings of Lead II from Dog 7 with "normal" electrocardiogram. No change occurred in the electrocardiogram during medication, although drug toxicity caused death after the first course of injections.

The absence of electrocardiographic changes in thirty-two of the thirty-nine dogs studied in this series is in accord with the experimental findings in other studies which have indicated that cardiac involvement is not a frequent side effect of chemotherapy. In spite of toxic reactions which were fatal in six cases, the conducting system as such was unaffected by the sulfonamides used (Fig. 4.) Even in the dogs with definite conduction defects in the controls, as shown by A-V block (Fig. 2), the drug did not further depress conduction, and the frequency of dropped beats was unchanged. The duration of the QRS interval remained

remarkably constant in each series (Fig. 1). This does not support Dozzi's[7] contention that the sulfonamides are "not apt to alter the rhythm unless there is some pre-existing irritability of the conduction system." It is difficult to evaluate his evidence of sulfonamide effects on cardiac function, namely, A-V nodal rhythm, since the electrocardiogram presented for comparison is obviously not normal and the patient gave a history of previous attacks of paroxysmal tachycardia which were probably also of A-V nodal origin. Rhythmicity was not significantly altered by the drug, and rhythm characteristics, such as the marked sinus arrhythmia in Dog 27 (Fig. 3), were unchanged throughout the experiment. P-R interval changes showed the usual correlation with rate changes (Fig. 1). We feel that the rate variations during medication were the result of systemic effects associated with toxicity such as variations in body temperature. This might explain the increased rate noted in the sulfapyridine group since hyperpyrexia has been frequently reported as a side effect with this drug. Unfortunately, daily body temperatures were not determined during these experiments but are now being recorded in subsequent studies.

Cardiac function was, however, affected in seven of the dogs as shown by changes in the electrocardiogram. S-T segment deviation and change in the direction of the T wave were transient in five of the animals but persisted after medication in only two, while prolonged conduction time persisted in one. Electrocardiographic changes of this nature indicate some change in the myocardium which alters its physiologic state. The morphologic changes in cardiac muscle found at autopsy on sulfonamide-treated patients[3,5] might be expected to give rise to such electrocardiographic effects. The absence of these changes in spite of the frequency of toxic reactions (in 82 per cent of the series) brings up the question of drug idiosyncrasy. The ability of the sulfonamides to act as sensitizing antigens and thus produce hypersensitivity reactions has been emphasized by Rich.[6] He feels that they thus resemble foreign serum and are responsible for vascular lesions of the periarteritis nodosa type, which may involve the heart. Evidence of cardiac function changes during hypersensitivity reactions has been presented by Fox and Messeloff[15] in a report of transient electrocardiographic effects (S-T segment deviation and amplitude depression) in a boy suffering from serum sickness after tetanus antitoxin. None of the changes which we observed in these animals occurred during the first course of the drug but made their appearance in the later courses after the first rest interval of ten days. Sensitization may well have occurred during this interval in these animals and the subsequent courses of treatment resulted in morphologic changes which gave rise to the electrocardiographic effects. This could only be proved by microscopic study since, at autopsy, careful examination failed to reveal any gross changes in the hearts and blood vessels even in the animals dying during medication.

The extensive use of the sulfonamides prophylatically as well as for minor infections affords an opportunity for widespread sensitization. The frequency of drug hypersensitivity reactions reported in the literature and the histologic evidence of the relationship of such reactions to cardiac and vascular lesions of

varying severity emphasizes the danger of producing such changes if chemotherapy is continued in the face of a hypersensitivity reaction. The possibility of impairment of cardiac function in the gravely ill patient is obvious. Electrocardiographic studies during treatment would give early evidence of cardiac involvement and further indication for stopping the drug to prevent permanent damage; Rich[6] has suggested that, as the hypersensitivity reaction is of the anaphylactic type, prompt withdrawal of the inciting antigen will halt the progress of the lesions. With this in mind, patients treated with sulfonamides are being followed electrocardiographically and will constitute a future report.

As a result of our observations on cardiac function during sulfonamide therapy, we would like to endorse French and Weller's[3] suggestion that cardiovascular function be frequently checked when patients are being given sulfonamides and that electrocardiographic studies might well parallel the course of treatment.

SUMMARY

The effect of various sulfonamide drugs on the electrocardiogram was studied in thirty-nine dogs.

Sulfonamide administration had no effect upon the cardiac muscle and conducting system which could be demonstrated by the electrocardiogram in thirty-two dogs (82 per cent of the number studied), even though eleven of these dogs showed conduction defects before treatment.

Electrocardiographic abnormalities consisting of slight S-T segment deviation and change in direction of T wave occurred in seven dogs during medication and indicated some myocardial involvement. These changes were transient and disappeared after drug administration was stopped in all except three cases. The possibility that these electrocardiographic changes were the result of morphologic changes in cardiac muscle caused by sulfonamide sensitization is discussed.

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Clinical Reports

EFFECT ON THE HEART OF AN OVERDOSE OF EPINEPHRINE

Report of a Case

Commander A. P. McGinty and Lieutenant Commander L. S. Baer
Medical Corps, V(S), United States Naval Reserve

THE effect of epinephrine on the heart and coronary arteries is still a controversial subject. Available literature reveals no case report wherein an overdose of epinephrine produced prolonged electrocardiographic evidence of myocardial injury. For these reasons it is considered worth while to report the following case.

CASE REPORT

C. W. C., a naval aviator, 29 years of age, gave a history of a recent recurrence of malaria. In an attempt to produce a smear of blood which would exhibit malarial parasites, an injection of 0.5 c.c. of a 1:1000 solution of epinephrine hydrochloride was ordered. At 10:15 A.M. on April 11, 1945, an intramuscular injection of 5.0 c.c. of a 1:1000 aqueous solution of epinephrine hydrochloride was given inadvertently. The patient immediately experienced a sensation of constriction in his throat, a feeling of fullness in his chest, precordial distress, and a severe headache. When seen one minute later by the medical officer, he was pallid and in acute distress. His radial pulse was almost imperceptible and the heart sounds were extremely rapid and irregular. Five minutes after the injection, his blood pressure was 120/80. After being in extreme discomfort for about ten minutes, he vomited and felt relieved. In thirty minutes his pulse rate was 140 per minute and regular. At the same time his blood pressure was 160/96. Six hours later his pulse rate was 102 per minute and he felt much better except for a severe headache.

Twenty-three hours after the injection he was admitted to a United States Naval Hospital complaining of a constricting pain in the low parasternal area, some dyspnea, and a left temporal headache. The physical examination revealed a temperature of 101°F.; pulse rate, 105 per minute; respiratory rate, 24 per minute; and blood pressure, 94/60. No abnormal cardiac signs were noted. Breath sounds were decreased over the lower portion of the left lung. X-ray films of the chest revealed increased parenchymal density adjacent to the right and left borders of the heart. The leucocyte count was 8,000.

On April 12, 1945, the day of admission, an electrocardiogram revealed an inverted T wave in Lead I, a sharply inverted P wave in chest leads CF_2 and CF_4, and a 2 mm. elevation of the S-T segment in Lead CF_2. The following day the T wave in Lead I was more deeply inverted and the T wave in Leads II and III were of greater amplitude. On April 27, the inversion of the T wave was less and there was no elevation of the S-T segment. By May 16 the T wave in Lead I

Statements made in this article are those of the authors and do not necessarily represent the views of the Navy Department.

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was diphasic and by June 9 (fifty-nine days after the injection of epinephrine) the electrocardiogram was within normal limits, with upright T waves in Lead I and upright P waves in the chest lead.

Clinically the patient improved rapidly. His temperature was normal the day after admission. By April 16 all chest symptoms had disappeared and on April 18 an x-ray film of the chest was normal. The erythrocyte sedimentation rate was 22 mm. per hour on April 17 and 17 mm. per hour on May 7. By May 8 the left temporal headache, the most persistent and last symptom, was gone and he was allowed to be out of bed. Further convalescence was uneventful.

COMMENT

After reviewing the recent literature, Levy[1] stated that there was still a difference of opinion regarding the action of epinephrine on the coronary arteries. Studies of the effect of suspending short sections of a coronary artery in a solution of epinephrine gave a diversity of reactions. Studies on the rate of coronary circulation in the intact heart and in the perfused heart showed a decrease in the rate of perfusion after small doses of epinephrine but increased cardiac activity and an increased perfusion rate after larger doses. Other observers reported that epinephrine caused an increase in cardiac rate and a decrease in the coronary flow. Epinephrine applied directly to the coronary arteries of the tortoise produced constriction of the vessels.

Sollman[2] stated that the constrictor effect of epinephrine was weak in the coronary arteries and that in the intact animal these vessels were passively dilated by the displacement of blood from the more powerfully constricted areas. Subsequently, he stated that clinically epinephrine probably caused coronary constriction and in most cases reduced the flow of blood through these arteries.

Levy[1] reported what many have confirmed: that 1.0 c.c. of a 1:1000 solution of epinephrine hydrochloride injected subcutaneously into a patient who has had angina pectoris will produce a typical attack of pain. This seemed to be evidence that epinephrine reduced the flow of blood through the coronary arteries.

Katz[3] listed epinephrine as a drug which may cause extrasystoles, depression of the S-T segment, and inversion or flattening of the T waves. He reproduced electrocardiograms from a case of angina pectoris which showed depression of the S-T segment in Leads I and II and a moderate flattening of the T wave in Lead I, sixteen minutes after the injection of 1.0 c.c. of a 1:1000 solution of epinephrine hydrochloride.

It has been stated by Katz[3] and Sigler[4] and in *The Epitome of the Pharmacopeia of the United States*[5] that toxic doses of epinephrine caused ventricular fibrillation.

SUMMARY

A naval aviator was inadvertently given an injection of 5.0 c.c. of a 1:1000 solution of epinephrine hydrochloride. The arrhythmia noted in the first thirty minutes could have been due to frequent extrasystoles or to transient ventricular fibrillation. The precordial distress, the transient elevation of tem-

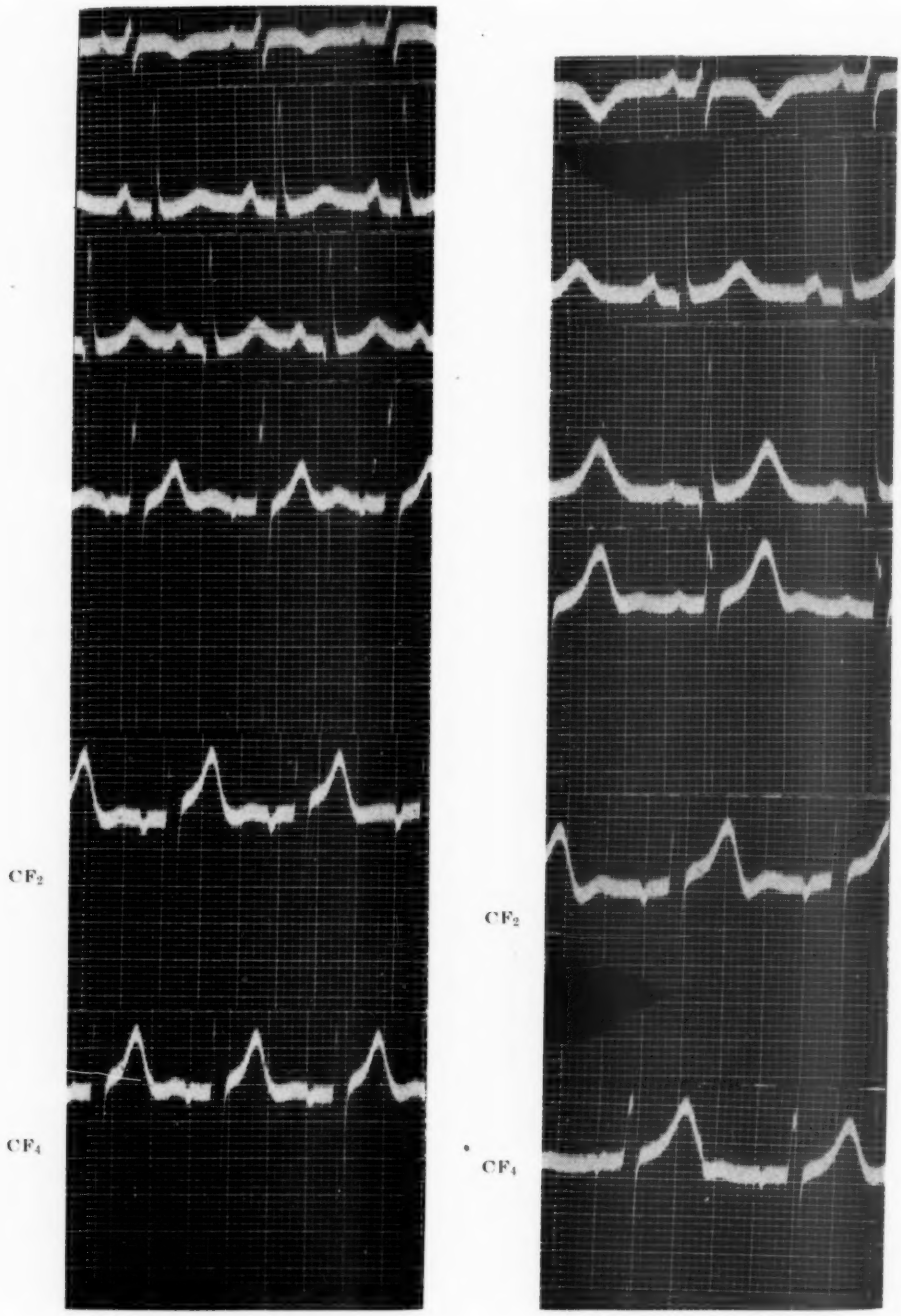

Fig. 1.—The first tracing was made twenty-three hours after the hypodermic injection of 5.0 c.c. of a 1:1000 solution of epinephrine hydrochloride. The last tracing was made fifty-six days after the drug was received.

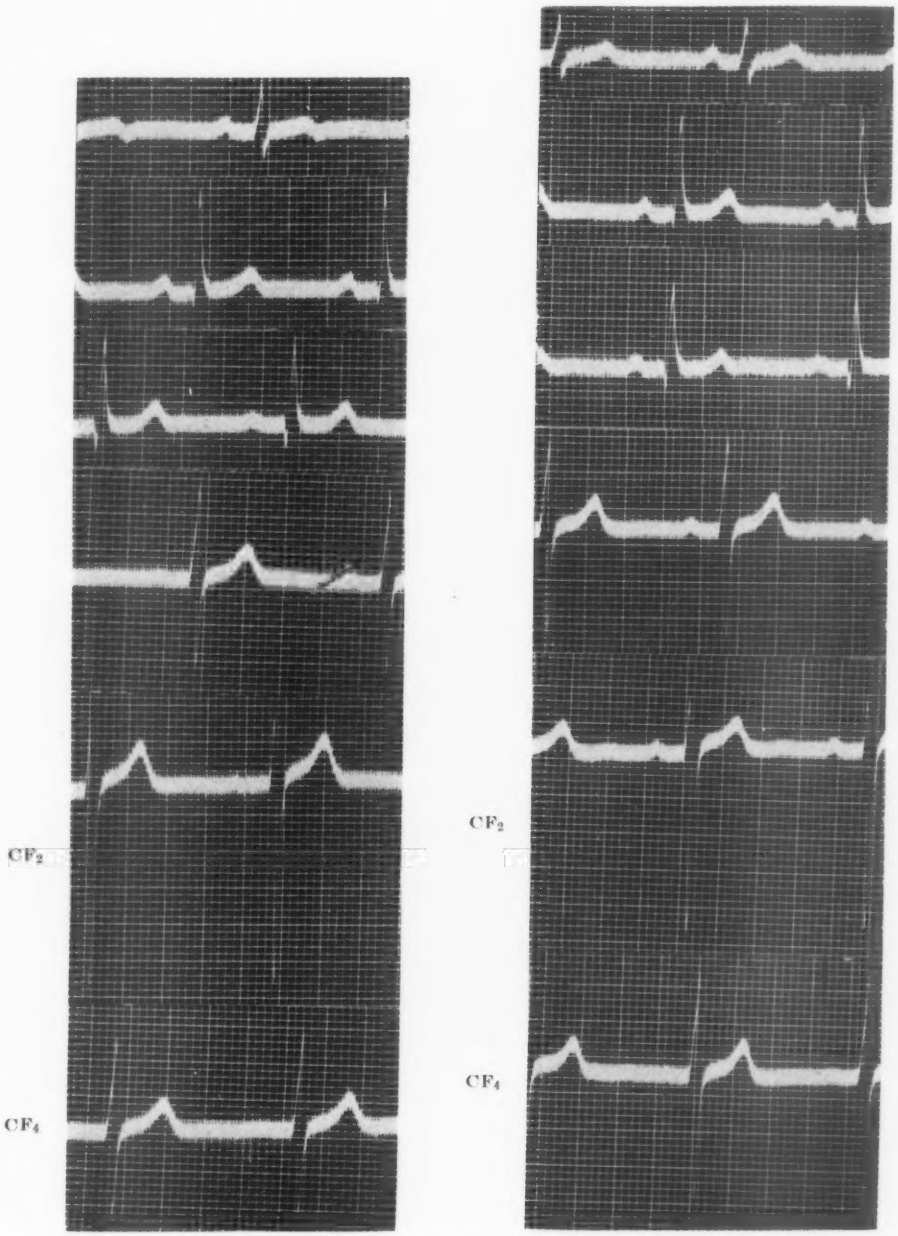

Fig. 1 Cont'd.—*(For complete legend see opposite page.)*

perature, the increase of sedimentation rate, and the prolonged electrocardiographic changes could have been due to actual infarction of the myocardium. The evidence in this case indicates that epinephrine in large doses causes relative coronary insufficiency in the normal adult.

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A CASE OF LARGE OVERDOSE OF EPINEPHRINE

ORVILLE HORWITZ, M.D.
PHILADELPHIA, PA.

RECENTLY I had the unfortunate experience of observing a patient suffering from urticaria who was given 7.0 c. c. of a 1:1000 solution of epinephrine. The physician in charge had ordered 7 minims and an apprentice, who mistook the order, administered 7 c. c. intramuscularly in the right buttock. Fig. 1 shows the result, which fortunately was not particularly dramatic. The error was dis-

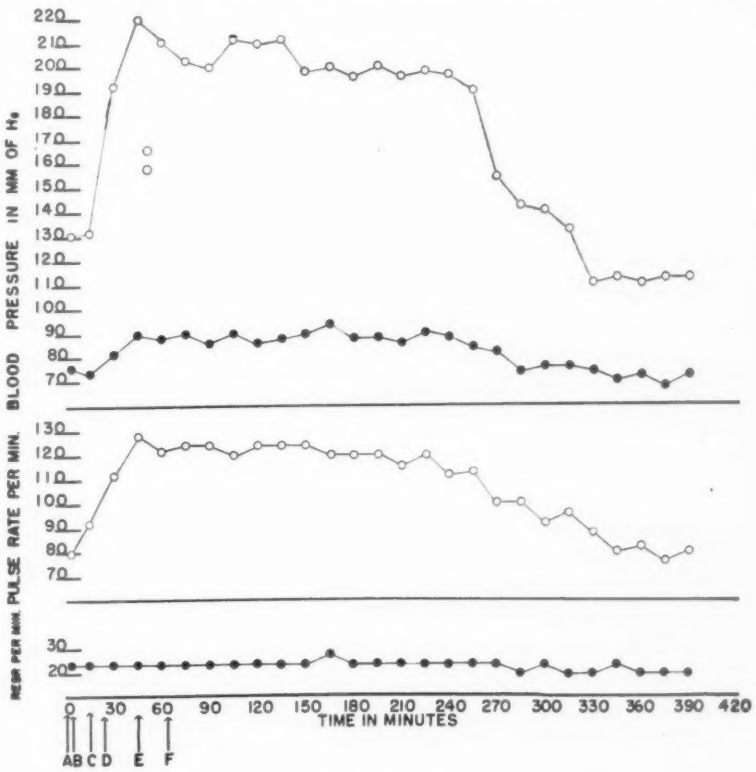

Fig. 1.—*A*, Administration of 7.0 c.c. 1:1000 solution of epinephrine intramuscularly in the right buttock. *B*, 0.4 Gm. sodium amytal administered by mouth. *C*, Patient put to bed with head elevated. *D*, Ice pack applied to site of injection with minimum of pressure. *E*, Patient developed mild headache. *F*, Patient given 0.6 Gm. aspirin and 0.03 Gm. codeine sulfate.

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covered immediately by a supervisor when the apprentice returned from the patient's room with a 10 c. c. syringe, attached to which was a No. 20 needle used commonly for intramuscular injections. The patient, a healthy adult male, 21 years of age, was treated, as shown in Fig. 1, by bed rest, sodium amytal, an ice pack applied to the site of injection with as little pressure as possible, and elevation of the head. He was completely undisturbed and unable to understand why he was being treated at all or why the blood pressure was being taken regularly at fifteen-minute intervals. His only symptom was a slight headache, for which he was given 0.6 Gm. of aspirin and 0.03 Gm. of codeine sulfate. There was no excessive perspiration and no cardiac arrhythmia observed at any time other than the mild degree of tachycardia noted in Fig. 1, of which the patient was barely conscious.* He did develop mild tremor. The highest blood pressure recorded at any time was 220/96. The pulse rate reached 128 per minute. The respiratory rate varied between 20 and 28 per minute. At the end of five hours blood pressure, pulse, and respiration had all returned to normal.

It was thought that the epinephrine must have caused considerable angiospasm at the site of injection, thereby allowing itself to be absorbed slowly by the systemic circulation over the five hours' time.

Two months later the patient was observed to have no apparent ill effects from his ordeal.

Incidentally, the dosage given ameliorated the urticarial condition.

SUMMARY

Seven cubic centimeters of a 1:1000 solution of epinephrine were administered to a patient intramuscularly in one dose. He had no immediate effects of a really violent nature and no permanent effects.

*It is unfortunate that the electrocardiograms which were made are no longer available. These tracings were carefully studied by competent physicians who could find in the tracings nothing except a moderate simple tachycardia and possibly a slight change (less than 1.0 mm.) in the height of the T waves.

CONGENITAL COMPLETE HEART BLOCK DIAGNOSED IN UTERO WITH SOUND TRACINGS AND SIMULTANEOUS ELECTROCARDIOGRAPH OF THE MOTHER

FRED C. JORDAN, M.D.,† AND HOWELL RANDOLPH, M.D.
PHOENIX, ARIZ.

THE infant was born of a primipara mother who was 33 years of age and in robust health. Five weeks before term it was noticed that the fetal heart sounds were extremely slow; they were counted at 40 to 46 per minute. It was thought that the life of the fetus was in danger, but after observation for several hours with no change in the heart rate no attempt was made to induce labor. During the subsequent ten days the fetal heart rate was always between 40 and 46 per minute. Sound tracings of the fetal heart was made simultaneously with the maternal electrocardiogram and are presented in Fig. 1.

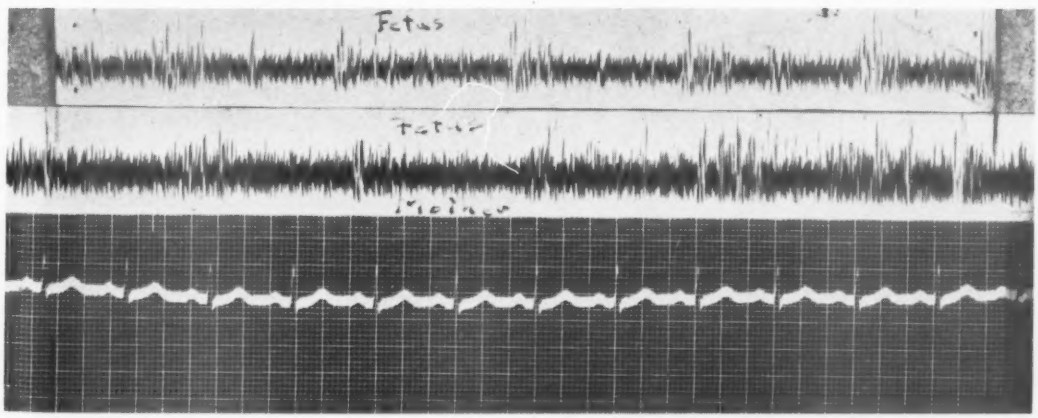

Fig. 1.—Sept. 11, 1944. *A*, Fetal heart sounds alone; rate, 48. *B*, Fetal heart sounds recorded synchronously with maternal electrocardiogram. The fetal heart rate was 48 per minute; the maternal heart rate, 95 per minute.

The mother was delivered at the beginning of the ninth month. The baby was an apparently healthy infant weighing 5 pounds, 12 ounces. Sound and electrocardiographic tracings made after delivery are shown in Fig. 2.

Since birth, the infant has presented a difficult feeding problem. Regurgitation of food is still frequent, yet fairly normal growth has taken place. At

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†Fred C. Jordan, M.D., died July 29, 1945.

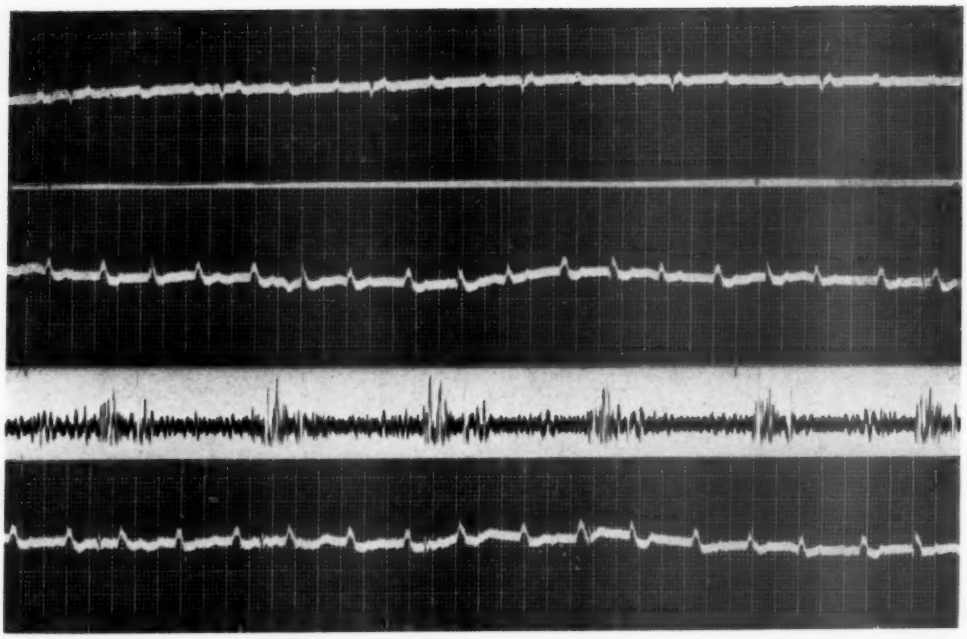

Fig. 2.—Sept. 14, 1944. Infant electrocardiogram and infant phonocardiogram recorded synchronously. Ventricular rate is 43 per minute; auricular rate, 124 per minute.

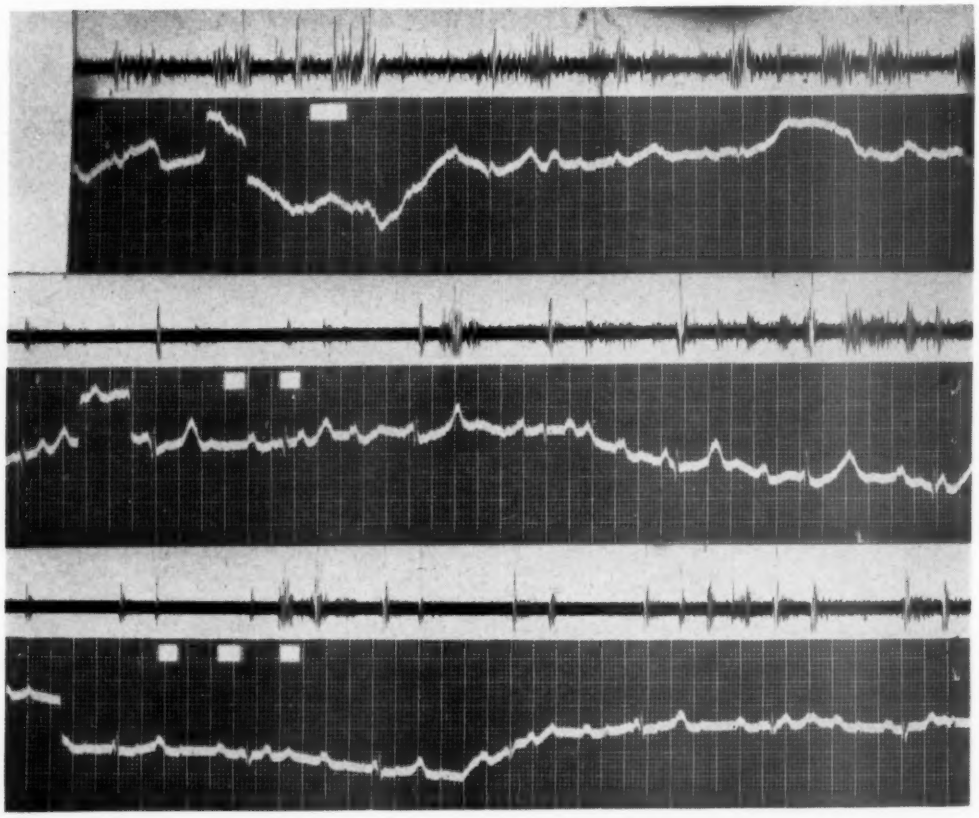

Fig. 3.—Sept. 4, 1945. It was technically difficult to take this tracing because of the constant movement of the infant. It shows complete heart block with disassociation of auricular and ventricular contraction. The graph remained about the same as that shown on the tracing taken at 2 days of age. The ventricular rate is 44 per minute; auricular rate, 130 per minute.

12 months of age the weight was 17⅛ pounds and the length, 29 inches. The lips were pale, the tissues somewhat flabby, and the skin rather loose. Eight teeth were present. There was no lymphadenopathy and the lungs were clear. There was a short definite systolic murmur audible at the apex and at the left third interspace. The second sound was distant and normal. These findings are recorded on the various phonocardiograph tracings, even on the tracing of the fetus taken in utero. The liver was not enlarged, the spleen was not palpable, and the extremities were normal. An electrocardiogram and a phonocardiogram made at the age of 12 months are shown in Fig. 3.

ARTERIOSCLEROTIC ANEURYSM OF THE CARDIAC CORONARY ARTERIES

Report of a Case

Nathan Mitchell, M.D.
Brooklyn, N. Y.

DESPITE the frequency and severity of involvement of the coronary arteries by atherosclerosis, true aneurysm formation resulting from this type of purely degenerative process is rare. The most recent comprehensive collection of cases of coronary artery aneurysms due to all causes is that of Packard and Wechsler.[1] Of thirty aneurysms discussed by them, seven were classified as "mycotic-embolic," while twelve were considered to be definitely arteriosclerotic. In the remaining eleven cases insufficient data were presented to permit of their accurate classification.

Since the report of Packard and Wechsler, additional single cases of atherosclerotic aneurysms have been presented by Eliasoph,[10] Cox and Christie,[11] Chiari,[12] Nagayo and Takahashi,[14] and Domenichini.[15] It is the purpose of this presentation to analyze the anatomic details of the aneurysms previously reported and to add an additional case.

REPORT OF CASE

The patient was a 42-year-old thin, spare, high-strung man. He was the proprietor of a music store and had been in good health until about five years before his last illness when he visited his physician for some minor complaint. A complete physical examination at that time revealed no evidence of hypertension or diabetes. He had felt perfectly well until his present illness.

About two weeks before his death he began to notice slight dyspnea and precordial distress after exercise. The final fatal illness was ushered in with the sudden onset of severe precordial pain radiating to the left arm, associated with "a heavy feeling on my chest, as if a sand bag had been placed there." The patient went rapidly into shock and expired about twenty-four hours later.

Autopsy was performed three hours after death. With the exception of marked pulmonary edema and congestion of the abdominal viscera, the pertinent findings were limited to the heart and the aorta.

The heart was slightly enlarged, weighing 380 grams. It measured 15 cm. from base to apex and 13 cm. in its widest diameter. A small partially organized fibrous tag bound the apex to the parietal pericardium. The epicardium showed moderate focal congestion which was especially prominent over the anterior longitudinal sulcus. On section of the left ventricular myocardium, a large, soft, well-demarcated red zone of discoloration was seen in the posterior two-thirds of the lateral wall. It measured 4 by 7 cm. in size. A similar but smaller focus of discolored myo-

From the Albany Hospital and Albany Medical College Laboratories, Albany, N. Y.
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cardium 3.1 by 2.5 cm. in size was present in the interventricular septum. The papillary muscles of the left ventricle presented some yellow opaque foci of infarction most prominent at their apices. The cardiac valves showed no abnormalities.

After dissection of the epicardial fat, the coronary arteries were exposed, and the unusual changes about to be described were disclosed. The left coronary artery arose from its usual site and measured 1.2 cm. in length. The anterior descending branch, as well as the main artery itself, showed extensive intimal plaque formation and moderate dilatation of the lumen. The circumflex branch was markedly sclerosed and the lumen, just distal to its point of origin, was narrowed to a pin-point opening by concentrically arranged yellow atheromatous plaques. At a point 1 cm. from the origin of this branch a large fusiform aneurysm measuring 2.4 cm. in length and 1.2 cm. in width was present (Fig. 2). The lumen of the vessel at the site of aneurysm formation was patent, and no mural thrombus was seen.

Fig. 1.—Saccular aneurysm of the right coronary artery, just distal to its first bifurcation. The subepicardial fat has been partially dissected.

The right coronary artery pursued a normal course in the right atrioventricular groove for a distance of 2.9 centimeters. At that point, just after the origin of a small vessel which supplied the apex of the right ventricle, a saccular aneurysm measuring 1.2 by 1.2 by 1.1 cm. was present (Fig. 1). The outer wall of the aneurysmal sac was markedly sclerotic and of a bright yellow color. The continuation of the right coronary artery beyond the aneurysm showed extensive intimal sclerosis with superimposed calcification and almost complete obliteration of the lumen.

Longitudinal section through the aneurysm of the right coronary artery revealed a saccular structure which was covered externally by slightly thickened adventitia (Fig. 3). The media had apparently been completely destroyed at the summit of the sac and the remainder of the aneurysm wall was composed of the bright yellow opaque atheromatous intima which showed foci of hemorrhage. Attached to the inner lining of the sac was a large grayish-brown thrombus which was spongy, granular, and translucent. The lumen of the vessel at this point appeared as a thin slit beneath the thrombus.

Microscopic examination of the heart revealed three foci of early infarction characterized by necrosis of the myocardial fibers, neutrophilic infiltration, and surrounding congestion. Moderate infiltration of the epicardial fat by neutrophiles was also present.

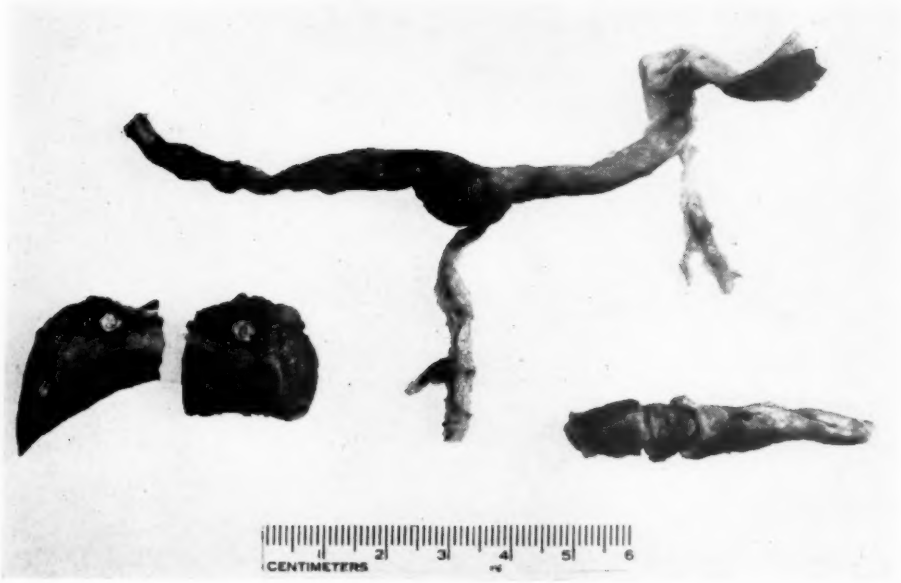

Fig. 2.—The right coronary artery and aneurysm are shown above. Below and to the left is a transverse section through the distal portion of the right coronary artery, showing almost complete occlusion of the vessel. Below and to the right is shown the fusiform aneurysm of the circumflex branch of the left coronary artery.

Fig. 3.—Longitudinal section through the saccular aneurysm showing the advanced atherosclerotic lesion in its wall and a large mural thrombus. Note the extensive atherosclerotic change in the remainder of the artery.

The coronary arteries were the seat of extremely advanced atherosclerosis. Large deposits of lipid material and calcium salts in many places almost obliterated the lumens of the arteries. Where the intimal plaques were most extensive, the underlying media was markedly thinned out. Sections through the wall of the saccular aneurysm revealed that at its widest portion the sac was covered externally by only a thin layer of fibrotic adventitia. The collagenous fibers of the adventitia in this section showed moderate hyalinization. Beneath the thin rim of adventitia the media had been completely destroyed and the thickened intima showed a wide zone of infiltration by lipid material and calcium salts. Focal collections of inflammatory cells, most of which were lymphocytes and plasma cells, were present adjacent to the accumulation of lipid material. Many foreign body giant cells were noted, some containing as many as sixty nuclei. The cytoplasm of some of the giant cells contained rounded globules and cleftlike deposits of lipid in addition to a few granules of light yellow-brown pigment which was probably hemosiderin. The brown pigment was also seen in the cytoplasm of isolated macrophages as well as extracellularly. A large, partially organized, recanalized mural thrombus occupied the largest part of the aneurysmal sac. The newly formed vascular channels were lined by markedly hyperplastic endothelial cells. In some places remnants of deeply eosinophilic fibrin were seen. Beneath the thrombus was a small slitlike lumen which was lined by endothelial cells. Where the aneurysm took origin from the vessel wall, remnants of atrophic and compressed muscle fibers of the media were still visible.

Sections of two bifurcations of the right coronary artery showed no defects in the muscularis. Preparations stained to show elastic tissue revealed no abnormalities of the inner elastic membrane in the grossly uninvolved portions of the coronary arteries. However, there was total destruction of this membrane in those branches of the right coronary artery where the atheromatous plaques were most prominent. No elastic fibrils could be found in the wall of the aneurysm.

The ascending aorta showed extensive atheromatous change. Many irregular, slightly raised, moderately indurated, broad, yellow plaques were present in its intimal coat. The plaques were present throughout the ascending aorta, extending proximally as far as the sinuses of Valsalva, where they surrounded both coronary ostia and produced partial stenosis of the right ostium (Fig. 4). The latter measured 0.2 cm. in diameter, whereas that on the left measured 0.5 centi-

Fig. 4.—Extensive intimal atherosclerosis of the ascending aorta, with involvement of the sinuses of Valsalva and partial stenosis of the ostium of the right coronary artery. These plaques were bright yellow in color. There is conspicuous absence of intimal wrinkling and stellate scars.

meters. The wall of the aorta showed no pearly-white plaques, intimal wrinkling, or thickening of the adventitia, changes such as are found in syphilitic aortitis.

Microscopically, the aorta showed marked intimal thickening and many foci of hyalinized collagen. Large deposits of lipid material, lipophages, fibroblasts, and focal areas of calcification were also noted. The media contained many focal collections of lymphocytes and in one situation neutrophiles were present. The adventitial fat was moderately and relatively diffusely infiltrated by lymphocytes.

The final anatomic diagnoses were as follows: aneurysms, saccular and fusiform, multiple, atherosclerotic, of coronary arteries; stenosis, partial, of right coronary ostium by atherosclerotic plaque; infarct, recent, of left ventricular myocardium and interventricular septum; atherosclerosis, marked, of aorta and coronary and pulmonary arteries; pericarditis, acute, slight; edema, moderate, of lungs; congestion, marked, of liver, spleen, and kidneys; necrosis, acute, focal, of liver; fibroma of left renal medulla; hemorrhages, recent, mucosal, of renal pelves.

COMMENT

Packard and Wechsler listed twelve cases of coronary artery aneurysms as definitely of arteriosclerotic origin but objection may be raised to the inclusion of the cases of Wood[17] and Martland[16] and to the exclusion of Toller's[13] case, which was classified by them as probably mycotic-embolic. Concerning the last case, they state that "unfortunately the condition of the heart valves is not mentioned," but reference to Toller's paper reveals that "the aortic valve contained dense masses of calcareous material, but there were no vegetations." The aorta showed extensive atheromatous change, and the right coronary artery "was diseased from end to end." The left coronary artery distal to the aneurysm was normal. In the absence of histologic examination of the wall of this aneurysm, no definite etiology can be said to be established, but from the evidence at hand it is probable that the case belongs in the group due to atherosclerosis.

In a discussion of a case presented by Clark before the New York Pathological Society, Wood[17] stated that he "presented to the society some years ago an aneurism of the coronary artery . . . .," but no formal reference to a published paper could be found. Martland's case was that of a 32-year-old Negro woman who died of cardiac tamponade secondary to a massive hemopericardium. There was an aneurysm of the supravalvular portion of the aorta measuring 2.5 by 4 by 1.5 centimeters. The pouch and the surrounding aorta for a distance of 4 cm. above the aortic ring showed a rubbery, irregular, but smooth appearance. The intima presented numerous grayish-blue hyaline, slightly raised areas, many of which showed small depressions or distinct puckered scars. In addition, there was a globular aneurysm of the right coronary artery arising immediately beyond the right coronary ostium. Martland concluded that "as regards the etiology of this lesion, we have undoubted gross evidence of a luetic mesaortitis." While it is true that "early and superimposed atherosclerosis" was present in the aortic aneurysm, no mention was made of any atherosclerotic change in the aneurysm of the right coronary artery.

If the revised interpretation of the listed cases is acceptable, there have been seventeen authentic cases of atherosclerotic aneurysm of the cardiac coronary arteries, including the five published since Packard and Wechsler's paper and the present one. All of these cases are listed in Table I.

TABLE I. FINDINGS IN THE SEVENTEEN REPORTED CASES OF ATHEROSCLEROTIC ANEURYSMS OF THE CARDIAC CORONARY ARTERIES

AUTHOR	AGE	SEX	CLINICAL HISTORY	SITE	SIZE	RUPTURE	CORONARY ARTERIES	REMARKS
1. Crisp	63	M	Sudden death	R	Walnut	Yes	Moderate atheroma	Atherosclerosis of aorta
2. Peste	77	M	Myocardial infarction	L	Large nut	Yes	Calcification	Rupture of left ventricle
3. Peacock	51	M	Cardiac failure	L	Pigeon's egg	No	Ossification of left, calcification of right	Fibrinopurulent pericarditis
4. Buchner	47	M	Sudden death	L	6 cm.	No	Bony plaques on floor of aneurysm	Fibrinopurulent pericarditis
5. Capps (a)	48	M	Found dead	L	Pigeon's egg	No	Calcification of left, atheromatosis of right	Atheromatosis of aorta
6. Capps (b)	39	M	Convulsions, bronchopneumonia	L	Hazel nut	No	Atheroma and calcification	No mention of proved syphilis
				L	Small hazel nut	No		
7. Winkler	68	M	.....	L	.....	No	Thickening and calcification	Scarring of myocardium
8. Sommer	73	M	.....	L	2 peas	Yes	Slight atheromatosis	Rupture of aneurysm into wall of pulmonary artery
9. Windholz	62	F	Cardiac failure	L	Nut	No	Paper-thin, hyaline deposits	
				L	Pea	No	Rigid walls, calcific plaques	
10. Packard and Wechsler	60	M	Found dead soon after anginal seizure	L	Pea	Yes	Marked atherosclerosis with calcification	Slight myocardial fibrosis
11. Toller	40	M	Cardiac failure	L	Hen's egg	No	Severe sclerosis of right coronary artery	Aortic valves calcified
12. Eliasoph	58	M	Cardiac failure	L	7 mm.	No	Marked atherosclerosis; dissecting aneurysm in wall in region of aneurysm	Ventricular aneurysm secondary to myocardial fibrosis
13. Cox and Christie	65	M	Cardiac failure	R	2.5 cm.	No	Marked atherosclerosis and calcification	Myocardial fibrosis
14. Chiari	34	M	Cardiac failure	R	10 cm.	Yes	Extensive atherosclerosis	Congenital widening of ostium
15. Nagayo and Takahashi	70	M	Cardiac failure	L	7 by 1 by 1.8 cm.	No	Extensive atherosclerosis	Myocardial fibrosis
16. Domenichini	77	M	Pneumonia; no cardiac symptoms	L	Nut	No	Severe atherosclerosis	.....
17. Mitchell	42	M	Myocardial infarction	R	1.2 by 1.2 by 1.1 cm.	No	Advanced atherosclerosis	Stenosis of right coronary ostium by atheromatous plaque of aorta
				L	2.4 by 1.2 cm.			

The single significant predisposing etiologic factor was the predominance of the male sex, all but one of the patients being men. The ages varied from 34 to 77, with a mean age of 57 years. The left coronary artery or its branches were involved in thirteen instances. In four cases the aneurysms were found in the right coronary artery. Multiple aneurysms were described in three cases, while involvement of both right and left coronary arteries was present only in the case herewith reported. The smallest aneurysm was the size of a pea, and the largest approached the size of a hen's egg in greatest diameter. Rupture of the aneurysm had occurred in five cases. Hemopericardium with cardiac tamponade resulted on three occasions. There had been perforation into the myocardium of the right ventricle in one instance and extension to the wall of the pulmonary artery in another.

The cause of death was apparently of cardiac origin in fourteen cases. Of these fourteen, seven deaths were attributed to progressive cardiac failure; two followed typical episodes of coronary thrombosis; two occurred suddenly at varying intervals after anginal seizures; and in two cases the patients were found dead, with no clinical history available. No data about the terminal phase of illness were furnished in one case, but death was presumably of cardiac origin. Of the three noncardiac deaths, two were attributable to pneumonia and one to cerebral hemorrhage.

Of the fourteen deaths of cardiac origin, only five can be traced directly to the aneurysm itself. In three of these instances, the aneurysm had ruptured into the pericardial cavity, and the resultant hemopericardium was the obvious mechanism of sudden death. The remaining two cases showed, respectively, rupture of the aneurysm into the myocardium of the right ventricle and into the wall of the pulmonary artery. The presence of the aneurysm may be considered only as a major contributing factor to the fatal outcome in the latter two cases. In the entire series, therefore, the aneurysm of the coronary artery appeared to be an incidental finding in twelve cases, and the clinical picture was caused either by advanced coronary atherosclerosis and its sequellae, or by extracardiac disease, such as pneumonia or cerebral hemorrhage.

Much work has been done in the past decade or so on the pathogenesis of aneurysms of the cerebral arteries comprising the circle of Willis and its major branches. Forbus[18] first called attention to the constancy of medial muscular defects at the bifurcations of these vessels in patients with so-called congenital or "berry" aneurysms. He found similar defects in the cerebral arteries in those without aneurysms. Forbus also studied the coronary arteries and found that two of nine cases examined showed medial muscular defects at the bifurcations. Glynn[19] later stressed the importance of the elastic layer of the cerebral arteries. By injection experiments, he noted that outpouchings were not formed at the site of artifically produced medial defects if the integrity of the elastica was preserved. Harris,[20] in a report of a case of aneurysmal dilatation of the coronary artery associated with a congenital anomaly, studied the elastic tissue of the coronary arteries. He observed deficiency of the elastic tissue of the coronary arteries and attributed the dilatation of the involved vessel to this condition.

In the patient reported on herewith, two bifurcations of the right coronary artery were examined and no medial muscular defects were observed. Elastic tissue stains revealed marked fraying of the elastica at the border of the saccular aneurysm and complete disappearance of elastic fibers within the aneurysmal sac. No defects in elastic tissue were seen in the apparently uninvolved portions of the vessels. These facts, taken together with the location of the aneurysms beyond the points of bifurcation, would tend to eliminate congenital defects as possible factors in the development of the aneurysms. The presence of advanced atherosclerotic changes in the walls of all branches of the coronary arteries as well as in the aneurysmal sac point to an exclusive role for atherosclerosis in the pathogenesis of the aneurysms described.

There is little doubt that the total destruction of the media in the portion of the right coronary artery which was the site of the saccular aneurysm was caused by the slowly enlarging intramural atheroma. Similarly, the aneurysm formation may be attributed to constant intra-arterial pressure exerting its effect on a weakened portion of vessel devoid of elastic fibers. Mural thrombosis and adventitial fibrosis at the summit of the sac only partially explain the absence of rupture in this instance. That the aneurysm did not rupture is probably a fortuitous circumstance and is explained largely by the patient's premature death from myocardial infarction. The infarct in this case was caused by diminished coronary arterial flow occasioned not only by progressive occlusive coronary atherosclerosis, but also by partial stenosis of the right coronary ostium by an aortic atherosclerotic plaque.

The rarity of aneurysms of the cardiac coronary arteries is due in great measure to the strategic nature of the coronary circulation. The frequency of thrombosis as well as hemorrhage into an atheroma with subsequent occlusion with or without thrombosis, together with the fact that coronary occlusion leads so frequently to an early fatal outcome, militate against the development of atherosclerotic aneurysms.

CONCLUSIONS

1. Atherosclerotic aneurysms of the cardiac coronary arteries occur rarely. From the available literature, only sixteen cases have been collected, and one additional case is reported.

2. The strategic nature of the coronary circulation which favors an early fatal outcome from coronary occlusion and myocardial infarction is offered as an explanation for the rarity of coronary artery aneurysms.

3. Aneurysm of a coronary artery is rarely the immediate cause of death. Of the seventeen patients, only five died as a result of rupture of the aneurysm; in the remaining twelve the aneurysm was apparently only an incidental finding.

4. Congenital defects can be eliminated as factors in the development of the atherosclerotic aneurysms of the coronary arteries presented in this paper, since the aneurysms were not located at the bifurcations of the arteries, no medial muscular defects were found, and widespread atherosclerotic changes were present

throughout the coronary arterial circulation as well as in the aneurysmal sacs. The destruction of elastic fibers at the site of atheromas is an important factor leading to aneurysm formation.

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CONGESTIVE HEART FAILURE AND DEATH IN A CASE OF PAROXYSMAL AURICULAR TACHYCARDIA

Case Report

Robert P. Grant, M. D.
New York, N. Y.

FROM the time of its first description in 1888 by Bristowe,[1] paroxysmal auricular tachycardia has been known as a slightly disabling, rarely fatal arrhythmia usually occurring in persons with normal hearts. In large series of patients with this disturbance, less than 1 per cent develop congestive heart failure and rarely among these does death occur.[2,3] It is a common clinical aphorism, therefore, that if heart failure supervenes during an episode of paroxysmal auricular tachycardia, there is underlying organic heart disease.[4] In the available literature only four cases could be found where death from congestive heart failure during paroxysmal auricular tachycardia occurred, and at autopsy no certain evidence of a previously existing heart disease was found.[5-8] In the most clearly described of these cases, the tachycardia had persisted for weeks or months when finally heart failure appeared, and then the hearts showed pathologically cellular infiltrations or recent infarction.

The following case is presented as an example of death from congestive failure shortly after onset of paroxysmal auricular tachycardia in a patient who had presented no clinical evidence of the advanced structural cardiac disease he was found to have at autopsy. The patient had, in fact, undergone a specially devised rigorous medical and physiologic examination before the episode and no abnormalty had been detected. This demonstrates that even when no clinical evidence of organic heart disease can be found in persons with parosysmal tachycardia, the appearance of heart failure shortly after the onset of the tachycardia makes organic disease of the heart a nearly certain diagnosis.

The patient was a 20-year-old private first class whose previous medical and family history were not known beyond the fact that rheumatic fever was denied and there had been no recent severe illness. In May, 1944, four months before onset of illness and after being judged medically sound by his medical officer, he was examined for "fitness for hard work" by examiners at the Harvard University Fatigue Laboratory* who were serving as consultants to the Office of the Quartermaster General of the United States Army in the selection of troops to test military equipment. The physiologic tests consisted of a "step test," in which the subject mounts and descends a two-stepped, twenty-inch platform at the rate of thirty ups and downs per minute to tolerance, and a four-mile forced march with full pack and gun. To both tests the patient's

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*Permission to present this data was generously provided by Dr. Robert C. Sterling, of the Fatigue Laboratory, who supervised the tests.

tolerance was "average": the pulse rate one minute after completing three and one-half minutes of the step test was 160; his elapsed time in the forced march was fifty minutes, forty-five seconds. Following the satisfactory completion of these tests, he was sent to his post where, during the succeeding summer months, he participated as a subject in the testing of rations and wearing apparel in simulated tropical combat conditions.

He had had no prior episode of palpitation and no recent illness when, on the morning of Sept. 6, 1944, after about three hours' walking on a routine thirty-mile hike, he first noted pounding of the heart. No other symptoms were experienced and he determined to finish the hike. Gradually weakness and shortness of breath became prominent and by late afternoon he was obliged to seek relief. He was brought to the camp dispensary by car. The "rapid pulse" was noted and after failure of carotid sinus pressure or gagging to slow it, he was given a sedative and put to bed in the dispensary. He slept fitfully and the next day continued to have a "tachycardia" of uncounted rate. By that afternoon dyspnea and restlessness were becoming marked and he was brought by ambulance to the hospital, a trying three-hour drive.

On admission he was in marked distress but was alert and responsive. He was orthopneic and cyanotic. Pink froth seeped from the corners of the mouth. Blood pressure and temperature were normal. Cardiac examination revealed the apex impulse to be within the mid-clavicular line, a perfectly regular rate of 200 per minute, and no audible murmurs. The lung fields were filled with moist râles and the jugular veins were distended. There was no edema or ascites. An electrocardiogram was immediately obtained which revealed supraventricular tachycardia of a rate of 240 per minute with erect P waves in all leads (Fig. 1).

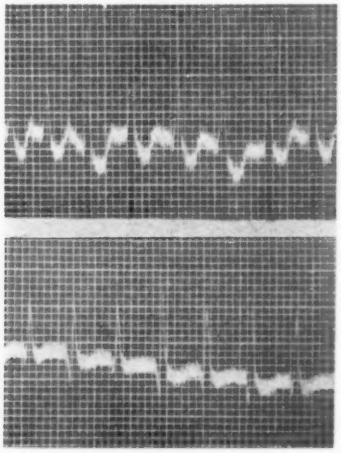

Fig. 1.—Electrocardiogram made approximately thirty-two hours after the onset of tachycardia. Only Leads II and III are available. The tracing shows a supraventricular tachycardia with a rate of 240 per minute.

Vigorous carotid and occular pressure were repeatedly applied without success; it was considered unwise to induce vomiting in view of the dyspnea. He was given 10 mg. of morphine sulfate hypodermically with some improvement and he drifted off to sleep. Four hours later, however, he again became dyspneic and the bloody froth reappeared. He was placed in an oxygen tent, a 500 c.c. phlebotomy was performed, intravenous digitalization was begun (0.4 Gm. initially, 0.2 Gm. at two-hour intervals thereafter), and tourniquets were applied to the limbs. Mecholyl and quinidine were not available. The patient never rallied; he died three hours later, or eight hours after admission and about forty hours after onset of the tachycardia.

Autopsy.—All organs and cavities were normal with the exception of the heart and lungs; the brain was not examined. Both lungs showed marked acute passive congestion with filling

of the entire bronchial tree with bloody frothy fluid; there was no evidence of consolidation. The heart weighed 400 grams; there was no significant dilation of chambers or hypertrophy of the myocardium; chordae tendineae and papillary muscles were intact. The mitral valve admitted one finger with difficulty and presented the typical "fishmouth" appearance of advanced mitral stenosis with thickened distorted valve edges mounted with small glistening gray nodules. There was an almost complete underlying band of calcification, and the attached chordae tendineae were moderately thickened. There was slight thickening of the edge of aortic valve cusps without separation of leaflets. The coronary arteries were patent throughout. Microscopic examination of the myocardium showed scattered small areas of fibrosis. No typical Aschoff bodies were seen. Impression: rheumatic fever, chronic, with marked mitral stenosis.

SUMMARY

A case of paroxysmal auricular tachycardia is presented which in a matter of hours led to acute congestive heart failure and terminated fatally. The case is of interest (1) because the patient had been tested rigorously medically and physiologically for work tolerance before the episode and was believed to be normal and (2) because the presence of the marked mitral stenosis could not be demonstrated before death. The diagnosis depended on the clinical aphorism, "paroxysmal auricular tachycardia leads early to heart failure only in the previously diseased heart."

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Abstracts and Reviews

Selected Abstracts

McGowan, J. M.: Cervical Rib: The Role of the Clavicle in Occlusion of the Subclavian Artery. Ann. Surg. **124:** 71 (July), 1946.

A study is reported of a series of cases of cervical rib in which it was found that a subclavian artery was intermittently occluded by mechanical pressure between the clavicle and the aberrant rib. In one of these cases the vascular disturbances were sufficiently severe to lead to gangrene of three digits of the right hand.

It has been generally believed that symptoms from cervical ribs are produced in many cases by pressure from the scalenus anticus muscle. This was found to be only partly correct by the author. The important structure of counterpressure is the clavicle. Vascular symptoms are produced by occlusion of the subclavian artery between the cervical rib and the clavicle. In the cases reported, the pulse was occluded partially or completely by the clavicle when the position of attention was assumed by the men.

In addition to crowding from a cervical rib and a hypertrophied scalenus anticus muscle, the costoclavicular state may be further narrowed by (1) elevation of the thoracic cage and (2) depression of the shoulder. The first condition is brought about by excessive use of the muscles of extraordinary respiration such as the sternocleidomastoid and the scalene group; and the second, by carrying a pack and by prolonged periods of standing in the position of attention. The longer the cervical rib, the greater the possibility of costoclavicular compression. Ribs 4 cm. or more are liable to be symptomatic. The more laterally placed the tip of the rib is, the more liable it is to produce symptoms. Right-sided cervical ribs produce symptoms four times more often than those on the left.

In three of the nine patients with cervical ribs that were operated upon, partial removal of the cervical rib was performed as well as a scaleniotomy. The results in the operated cases were all good.

NAIDE.

Harken, D. E.: Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart. Surg., Gynec. & Obst. **83:** 117 (July), 1946.

The danger of erosion and suppuration attending large retained missiles in relation to thoracic blood vessels is real. Three deaths from massive hemorrhage due to erosion have come to the attention of the author. Approximately 15 per cent of the thoracic vessel foreign bodies in the series presented have been associated with abscess formation, over 30 per cent were associated with other foreign material such as cloth or bone, and 67 per cent showed pathogenic bacteria on culture. It is, therefore, the author's policy to remove all foreign bodies measuring 1 or more centimeters in two dimensions. The technical difficulty of finding such fragments with operation are insignificant. In only one instance was there failure to remove a fragment.

Seventy-eight foreign bodies have been removed from within, or in relation to, the thoracic great vessels. Three of these were embolic. One of the three embolic bodies lodged in the left

pulmonary artery, another travelled from the heart to lodge in the innominate artery, and the third shifted from the left to the right pulmonary artery. All of these were removed without incident and with restoration of vascular continuity. Another series of fifty-six foreign bodies that have been removed from within or close to the heart is discussed. Thirteen of these were removed from the chambers of the heart. Indications for the removal of foreign bodies in great vessels and from the heart are discussed, and the salient features of cardiac exposure are presented. Various techniques and approaches are outlined for removing foreign bodies from the chambers of the heart.

The author emphasizes that the mortality and morbidity rates for retained foreign bodies in and in relation to thoracic blood vessels and the heart have not been completely assessed. However, in this series of 134 patients who have had foreign bodies removed, there were no deaths and the men are clinically well.

NAIDE.

Junco, J. A.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba: 1. The So-Called Borderline Case. Rev. cubana de cardiol. **6**:143 (July-Dec.), 1945.

Vitamin B deficiency appears to be very common among the children of Cuba, especially among the poorer classes whose chief dietary component is maize. Several clinical forms have been described: (1) the borderline case; (2) the acute beriberi of the nursling; (3) pellagra-beriberi of childhood; (4) idiopathic cardiac hypertrophy.

The borderline case of vitamin B deficiency occurs in children of all ages and is characterized by bizarre symptoms referable to the gastrointestinal, nervous, cardiovascular, and cutaneous muscular systems. These may be vague and often defy strict classification. Hydrolability is a characteristic, appearing either as edema or dehydration.

Cardiac disturbances were found in 75 per cent of the cases studied. They consisted of dyspnea, tachycardia, muffled first sound, embryocardia, and, at times, gallop rhythm. Murmurs, arrhythmias, and cardiac enlargement were conspicuously absent. Serial electrocardiograms showed sinus tachycardia, low voltage, and low amplitude T waves in all leads, indicating myocardial damage. Both the clinical picture and the electrocardiogram returned to normal following adequate thiamine therapy, indicating that the cardiac changes were reversible and due to deficient intake of vitamin B_1.

GOLD.

Abrilli, A. J.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 2. Acute Beriberi of the Nursling. Rev. cubana de cardiol. **6**: 156 (July-Dec.), 1945.

Acute beriberi in the nursing infant in Cuba has been found to be more common than such childhood diseases as pyloric stenosis, intussusception, scurvy, and tetany. Abrilli reports on fifty-two infants, most of whom were between 3 and 4 months of age. The majority of them were breast fed but received inadequate feeding. The mothers had been receiving inadequate diets although none had clinical beriberi. The onset of the disease was abrupt and was usually precipitated by a minor upper respiratory infection. The symptoms were characterized by disturbances of the nervous and cardiovascular system and were toxic in origin.

The cardiovascular changes were present to some degree in all forms of the disease; in some these changes were the dominant feature. Labored breathing, cyanosis, pulse rates of 120 to 190 per minute, distant heart sounds, and tic-tac rhythm were observed. Occasionally true gallop rhythm was seen. In only one case was a systolic apical murmur heard. There were no arrhythmias, and no arterial bruits were observed as reported in adult beriberi. The peripheral veins were collapsed; the radial pulse was weak and of low volume. The liver was moderately enlarged, and basal râles were heard in 10 per cent of the cases.

T-wave changes in Leads I and II were always present. These waves were flat or diphasic; in one case they were inverted. In most cases the QRS complex was of low amplitude with alterations of the S-T segment.

Of the fifty-two cases, ten patients died, two because of intercurrent infection, the remainder as a result of inadequate treatment. The response to thiamine intravenously was spectacular. The symptoms and signs disappeared within a few hours; however, cardiac hypertrophy often took days or weeks to disappear. At necropsy, the heart was always found to be enlarged as a result of dilatation and hypertrophy. The myocardium was soft and flabby. The right auricular walls were not atrophied and the pulmonary conus was never distended. Histologically, interstitial edema with separation of muscle fibres and vacuolization of the latter was found. Round cell infiltration was observed in one case. The endocardium and pericardium were not involved.

It was concluded that there was no relation between the cardiac disturbance and the acidosis frequently present. The latter was associated with marked excretion of organic acids of the pyruvic acid type. There was no ketonuria which distinguishes this type of acidosis from the ordinary ketosis.

GOLD.

de los Reyes, R. P.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 3. The Pellagra-Beriberi Syndrome. Rev. cubana de cardiol. 6:174 (July-Dec.), 1945.

The following clinical manifestations are present in the pellagra-beriberi syndrome: faulty development with loss in weight and height; cutaneous changes; mucosal pathology, especially of the tongue, mouth, palpebral, gastrointestinal, and vaginal tracts; gastrointestinal disorders (anorexia and diarrhea); disorders of the nervous system (changes in temperament, catalepsy, marked asthenia, abnormal reflexes); altered water metabolism (peripheral edema with a marked tendency to anhydremia); hepatic insufficiency; anemia, either hyperchromic, macrocytic, or hypochromic microcytic in type; change in the quality of the hair.

Cardiologic study revealed the same electrocardiographic findings reported by Junco and Abrilli (1 and 2), but cardiac enlargement was not found in the majority of the patients. In some cases, the heart was slightly enlarged, in others it was normal, and in several, the heart was small.

Reyes also studied the cardiologic changes in a control group of children suffering from anemia (parasitic, aplastic, posthemorrhagic and sickle-cell). The contrast with the pellagra beriberi heart of childhood was striking. In the former there was an almost consistent dilatation of the heart (either of the left or global) and frequent absence of electrocardiographie changes. Twenty-seven of the thirty-four patients studied had normal electrocardiographic tracings; of the other seven, five had tracings that resembled, somewhat, those seen in pellagra-beriberi, and in two there were marked alterations (one had A-V heart block). In addition, cardiac murmurs were the rule in this anemia group.

GOLD.

de la Torre, H.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 4. The So-Called Idiopathic Cardiac Hypertrophy. Rev. cubana de cardiol. 6:191 (July-Dec.), 1945.

De la Torre reports six cases of idiopathic cardiac hypertrophy and calls attention to the possible etiologic role of vitamin B_1 deficiency. This is predicated upon the similarities in the clinical picture obtained in this disease and that of infantile beriberi. The cardiac findings are much alike in both disorders except that the enlargement of the heart (particularly of the left chamber) is much greater in the former. However, important differences exist between them. At autopsy, two of the cases of idiopathic hypertrophy showed endocardial fibrosis. In addition, one case also had marked proliferation of the interstitial connective tissue. A third autopsy also revealed marked cellular infiltration, proliferation of the connective tissue, and small vessel dilatation with focal compression of the muscle fibres. Such changes were never found in the

heart of acute beriberi. Finally, the therapeutic response of four patients to adequate doses of vitamin B_1 was considered satisfactory at one stage or another of the disease, but the size of the heart was not materially affected by the therapy and a great tendency toward relapse was noted. According to de la Torre, this is perhaps best explained on the basis of irreversible changes due to the degree and duration of vitamin B_1 deficiency encountered in these cases of idiopathic cardiac hypertrophy as compared to the acute beriberi of the nursing infant.

GOLD.

Owen, G. C., and Bradford, H. A.: The Prothrombinopenic Effect of Massive Salicylate Therapy in Acute Rheumatic Fever. Ann. Int. Med. **25:** 97 (July), 1946.

Because of conflicting reports regarding the behavior of prothrombin activity in patients receiving large doses of salicylates, these authors undertook a study to determine the behavior of prothrombin in twenty-five patients with acute rheumatic fever treated by Coburn's method with large doses of salicylates. Their ages ranged from 18 to 40 years. All had been hospitalized for rheumatic fever in an acute state. The patients were given 10 Gm. of sodium salicylate in 1,000 c.c. of normal saline intravenously over a four-hour period daily for six days or longer, depending on the patient's clinical course. Those patients who failed to show a prompt response in symptoms, fever, and sedimentation rate were given an additional 10 Gm. of sodium salicylate daily. Thereafter, 10 Gm. of the drug were given orally each day in divided doses at four-hour intervals. Duration of treatment varied from twenty-one to sixty days. The Magath modification of the Quick method of determining the prothrombin time was used in these studies. By means of quantitative blood salicylate analyses made at three-day intervals, it was determined that concentrations of the drug were maintained at about 35 mg. in almost all cases.

Two effects of massive salicylate dosage on the blood prothrombin time were noted. A moderate prolongation of the prothrombin time occurred in all cases after the third or fourth day of treatment. Despite continuation of salicylates, there was a spontaneous and rather rapid return of the prothrombin time toward normal level. This tendency was noted as a general trend following the third week of therapy when the prothrombin time approached normal values despite the maintenance of high level of salicylate concentration in the blood. In five cases, bleeding, consisting of epistaxis or small nail bed hemorrhage, occurred at the time of maximum prolongation of the prothrombin time.

WENDKOS.

Lenegre, J., and Maurice, P.: First Recording of the Curves of Right Auricular and Ventricular Pressure in Man. Arch. d. mal. du coeur. **39:** 24 (Jan.-Feb.), 1946.

The graphic registration of the pressure in the right auricle and ventricle in ten subjects is reported. The technique involved the introduction of a catheter into an antecubital vein and its passage into the auricle and ventricle. The end of the catheter was connected to a piezograph in such a manner that the pressure waves were transmitted to the surface of a variable condenser. This in turn was connected to a cathode ray oscillograph which recorded the curves.

It was found that in a subject who had no cardiac abnormality, the differential ventricular pressure was 23 mm. Hg, or 31 cm. water. The differential ventricular pressure varied considerably, however, in the presence of cardiac abnormality. It was normal or only slightly increased when the cardiopathy was well tolerated but extremely high when the cardiopathy was poorly tolerated. Occasionally it was very high, even when the mean pressure was scarcely changed. Marked variations in the differential pressure occurred when the catheter was near the tricuspid valve.

Differential pressure in the right auricle varied from 6 to 10 mm. of mercury.

The shape of the ventricular pressure curve during diastole was, in some cases, almost horizontal, while in others it was clearly ascending. During systole the plateau of the curve may be ascending, descending, or dome shaped. The auricular shock was sometimes very clear, but at other times indistinct.

It is pointed out that the number of cases studied is not yet sufficient to give very definite significance to the various forms of the curves which were recorded.

LAPLACE.

Wastl, H.: Influence of Two Thiourea Derivatives on Blood Pressure in Hypertensive Rats. Arch. internat. de pharmacodyn, et de thérap. **71:** 204, (Dec. 31), 1945.

This investigation involved a study of the influence of S-benzyl-iso-thiourea hydrochloride and S-methyl-iso-thiourea sulphate on the blood pressure in experimentally induced hypertension in rats.

The rats were rendered hypertensive by looping a cotton thread over the poles of both kidneys. The blood pressure was measured in the tail of the unanesthetized rat by the plethysmographic method. During the period of treatment with the drug which was administered intraperitoneally in aqueous solution, the blood pressure dropped in many of the hypertensive rats but not in the normal control rats. In the hypertensive rats, the extent of the blood pressure decline varied individually according to the degree of hypertension and according to the dose of the drug.

The optimum dose for both compounds was 0.5 mg. per kilogram. With this dose, the average blood pressure of all hypertensive animals declined from the first to the fourth day of treatment. The blood pressure returned to its preinjection level by the third day after cessation of the injections. The reduction of blood pressure was more pronounced with increasing degrees of hypertension. Of the two preparations, the S-benzyl derivative exhibited a more pronounced depressor action. Both compounds showed a certain degree of tachyphylaxis in the later days of the experiment. No trace of any adverse effect was observed.

It is suggested that in cases of essential hypertension in man, 1 mg. per kilogram of S-benzyl-iso thiourea hydrochloride be administered orally.

LAPLACE.

Anrep, G. V., and Misrahy, G.: Ammi Visnaga as a Coronary Vasodilator. Gazette of the Faculty of Medicine, Cairo, Egypt (June), 1945.

The Khellin plant, which grows widely in Egypt, yields the drug *Ammi visnaga*. Of the principals extracted from *Ammi visnaga*, Visaminin proved to be the most important, and its action on isolated organs and on the whole animal was studied in detail.

Visaminin was found to have diuretic properties and proved capable of producing a relaxing effect on smooth muscle. In animals, intravenous administration caused a transitory fall in the blood pressure. In the heart-lung preparations, the authors found that Visaminin produced considerable increase in the coronary blood flow. They also found that 120 times the minimal amount necessary to produce coronary dilatation had no injurious effect on the heart muscle. No electrocardiographic changes were noted. The pulmonary blood pressure and the rate of the denervated heart were not affected.

The authors suggest the use of Visaminin in clinical practice as a coronary vasodilator and believe that it may prove to be superior to the caffeine and nitrite groups of drugs because of the prolonged action on the coronary arteries and because it does not lower the systemic blood pressure.

BELLET.

Kenawy, M. R., and Barsoum, G. S.: Ammi Visnaga in the Treatment of the Anginal Syndrome. Gazette of the Faculty of Medicine, Cairo, Egypt, **13:**33 (June), 1945.

As a result of the experiments of Anrep and Misrahy, which showed that this drug is an exceptionally strong coronary vasodilator, it was decided to test its effect upon patients with the anginal syndrome. Six patients with angina pectoris were subjected to exercise tolerance tests. Electrocardiograms were taken before and following these tests, after which the drug was administered orally and intramuscularly. Considerable improvement was observed in the patients'

symptoms and signs, and in some instances the anginal seizures were abolished for long periods of time.

The authors believe that this drug has a selective effect on the coronary blood vessels and does not lower the blood pressure in man. In two cases, depression of the RS-T segment disappeared following the administration of Visaminin.

BELLET.

Neuhauser, E. B. D.: The Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels. Am. J. Roentgenol. **56**:1 (July), 1946.

Symptoms of dysphagia, wheezing, stridor, or recurrent tracheobronchitis or pneumonia are indications for careful roentgenologic examination for anomalies of the great vessels. These congenital defects are not rare and are now, in many instances, amenable to cure or improvement by surgical intervention.

In addition to situs inversus, two types of right aortic arch without inversion are described. In the anterior type the aortic arch is anterior to the trachea and the descending aorta is on the right side. In the posterior type the aorta passes to the left behind the esophagus and the descending aorta is on the right of the normal left-sided position. On roentgen examination, the anterior right arch without inversion is found to produce a defect on the right side of the esophagus. There is no defect on the posterior aspect of the esophagus. This type of arch deformity alone does not produce symptoms.

The posterior right aortic arch may be of three types. In the first type, the left subclavian artery arises last from the arch and crosses behind the esophagus. In the second type, no vessel arises from the arch to cross the midline posterior to the esophagus. In the third type, there is a persistent left aortic diverticulum giving origin to the left subclavian artery. The basic deformity in the posterior right aortic arch consists of deviation of the esophagus to the left, a rounded defect on the right lateral aspect of the esophagus, and a rounded defect on the posterior aspect of the esophagus.

Double aortic arch of the constricting type produces a rather characteristic clinical picture in infants, although the diagnosis rests solely on roentgenographic examination. The onset of symptoms usually occurs in infancy and the patients with this syndrome usually present stridorous breathing, mild dysphagia, head retraction, chronic cough, and frequent attacks of pulmonary infection. The stridor is usually made worse by feeding. Four cases of this type from the Children's Hospital in Boston are reported. In these cases, no abnormality could be detected in the posteroanterior projection without the aid of contrast substance, since it is extremely difficult to visualize the position of the aortic arch in infants. In the lateral projection, it is impossible to see narrowing and anterior displacement of the trachea at the level of the aortic arch while the posterior right arch produced forward displacement of the barium-filled esophagus. The anteroposterior projection reveals narrowing of the esophagus from both the right and left sides due to pressure of the vascular ring, but there is no deviation of the esophagus to the left as seen with right aortic arch alone. A deformity of the trachea is likewise seen after the introduction of an opaque oil. The trachea is displaced forward at the level of the right aortic arch and is narrowed from both the right and left sides by pressure of the vascular ring, and pressed upon anteriorly by the left aortic ring.

BELLET.

Matthewson, F. A. L., and Sellers, A. H.: Electrocardiograms of Older Pilots. J. Aviation Med. **17**:207 (June), 1946.

Electrocardiographic data were collected on a series of 328 fliers who were 35 years of age and over. Analysis of the records revealed that ten of this group showed premature beats which were auricular in two instances and ventricular in eight. Ten showed a prolongation of the P-R interval slightly in excess of 0.20 second; six showed a P-R interval of 0.22 second or greater; and at least two exhibited the Wenkebach phenomenon. In seven fliers, the QRS interval was in excess of 0.10 second. Twelve showed deep Q waves, which were present in Lead I in three instances and in Lead III in nine. There were no instances of inversion of T waves in Leads I or II.

In the entire group, probable heart disease was detected by electrocardiography in two subjects. One of these showed left bundle branch block and the other showed abnormal T waves in Leads I and IV.

BELLET.

Lester, D., Lolli, G., and Greenberg, L. A.: The Fate of Acetylsalicylic Acid. J. Pharmacol. & Exper. Therap. **87**:329 (August), 1946.

This investigation deals with the behavior of the smaller doses of acetylsalicylic acid used as analgesics. It includes a study of the excretion, the forms, and concentrations in which salicylate appears in the plasma; the influence of bicarbonate upon absorption, plasma concentration, elimination, and accumulation of salicylate; the binding of salicylate by plasma; the distribution of salicylates in the body fluids; and the nature of the excretion of salicylates by the kidneys. Salicylate analgesia is also discussed.

The subjects were men who were mainly healthy laboratory personnel. The duration and amount of excretion of salicylate in the urine were determined after oral administration of 0.33 to 1.95 Gm. of acetylsalicylic acid. From 52 to 75 per cent of the acetylsalicylic acid ingested was found to be excreted in the urine in various forms. The time required for excretion ranged from fifteen hours for doses of 0.33 Gm. to thirty hours for doses of 1.95 Gm. The maximum concentration of total salicylate in the plasma was of the order of 4 mg. per cent after doses of 0.65 Gm. The plasma concentration bore an approximately linear relationship to the dosage.

The coincident administration of bicarbonate increased the rate of absorption of acetylsalicylic acid. This action does not alter the level of the maximum concentration that is reached in the plasma but does enable the maximum concentration to develop earlier. Bicarbonate also increased the rate of elimination of salicylate and hence the rate of decrease in concentration after the attainment of the maximum level.

In patients with rheumatic fever who are receiving salicylate therapy, a much lower per cent of salicylate is bound by the plasma than in normal individuals. In one instance only 6 per cent was bound at a total plasma concentration of salicylic acid of 37 mg. per cent. The binding of salicylate with protein decreases with decrease in concentration of protein, but the ratio increases and varies linearly with the concentration of protein.

Temperature exerts no effect upon the extent of the binding of the salicylate by protein. It was found that the binding power of plasma for free salicylate is much higher than for acetylsalicylate. The distribution between the plasma and the red cells and the peritoneal saline and cerebrospinal fluid was determined by the unbound fraction of plasma water. Acetylsalicylic acid is rapidly hydrolyzed after absorption, but up to a period of one to two hours as much as one-quarter of the salicylate in the plasma may be in the acetylated form.

The theory is advanced that the analgesic action of the acetylsalicylate is exercised mainly by the unhydrolyzed acetylated fraction in the plasma. If this hypothesis regarding the analgesic action is valid, the simultaneous administration of bicarbonate would have a beneficial effect in hastening the absorption and therefore speeding the analgesia. Since the duration is relatively short, a more rapid excretion of the salicylate caused by the bicarbonate may be advantageous.

BELLET.

Battro, A., and Mendy, J. C.: Precordial Leads in Children. Arch. Int. Med. **78**:31 (July), 1946.

These authors performed electrocardiographic studies on fifty healthy children whom they divided into three age groups: A (up to 2 years), B (3 to 5 years), and C (6 to 10 years). Besides the standard leads, six precordial leads (V_1, V_2, V_3, V_4, V_5, and V_6), as well as the unipolar limb leads (V_R, V_L, and V_F), were recorded by using the Wilson terminal electrode. In Group A, the R wave was often greater than the S wave in Lead V_1. This predominance of the R wave frequently persisted through Lead V_5, and thus differed appreciably from the findings in the precordial electrocardiogram of the normal adult. In Group B, the R and S waves tended to be

of equal amplitude in leads to the left and the right of the sternum. This finding in children of this age represents a form of transition between the configuration seen in Group A and that found in Group C. In Group C, the relative size of the R and S waves was fairly similar to the "adult type," with definite predominance of the S over the R wave in Lead V_1 and of the R over the S wave in Lead V_6.

The alterations of the T wave were as follows: in Group A, the T waves were frequently negative or diphasic even through Lead V_6. In Group B, negative or diphasic T waves were observed through Lead V_6, although this configuration was less frequently observed than in Group A. In Group C, negative T waves were not observed in Leads V_5 and V_6. The degree of negativity of the T wave usually decreased gradually in the three groups from Leads V_1 to V_6, with the exception of V_2, in which the negativity sometimes was greater than in Lead V_1.

BELLET.

Ravin, A., and Geever, E. F.: Coronary Arteriosclerosis, Coronary Anastomoses and Myocardial Infarction. Arch. Int. Med. **78:**125 (August), 1946.

The authors examined 166 hearts by the Schlesinger method. This technique involves cannulation of the right and left coronary arteries of the unembalmed heart and injection of a mixture of agar and a lead salt into these arteries. The mass injected into the respective arteries was given a different color. The injected mass passes through arterioles 40 microns in diameter and reaches about 50 per cent of the vessels 20 microns in diameter. Except for instances in which the diagnosis was obvious, the series was unselected and included a wide range of pathologic conditions as well as many normal hearts.

The ages of the patients varied from 1 to 90 years, the majority being in the range of 40 to 70 years. The failure of the colors to mix indicated that in the normal hearts, at least, there were no anastomotic vessels greater than 20 to 40 microns in diameter. When anastomotic vessels greater than 20 microns in diameter were present, the masses and their colors were mixed.

Interarterial anastomoses were found in thirty-six hearts. Occlusion of the coronary arteries was found in eighteen hearts. Seven specimens revealed more than one occluded vessel. Occlusion without infarction was present in five hearts and occlusion with infarction, in thirteen hearts. Infarction without occlusion of a coronary artery was observed in two hearts.

BELLET.

Errata

In the September, 1946, issue of the AMER'CAN HEART JOURNAL two errors appeared which we wish to correct:

In the abstract of the paper entitled "Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope," Am. J. Roentgenol. **54:** 217 (Sept.), 1945, the names of the two authors should read Henny, G. C., and Boone, B. R., instead of Henry, G. C., and Boone, A. A.

The phrase at the end of the fourth line of the second paragraph should read "*without distortion*" instead of "with distortion."

Book Reviews

RENAL HYPERTENSION. By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan Muñoz, and Alberto C. Taquini. Translated by Lewis Dexter. Springfield, Ill., 1946, Charles C. Thomas, Publishers.

By making this book available in English, Dr. Dexter has performed a great service to clinicians and experimenters interested in the subject of hypertension. By permitting Dr. Dexter to incorporate his own ideas and to include the additional work that has been performed on this subject since the appearance of the first edition, in 1943, in Spanish, the authors have enabled him to bring the whole subject up to date. Although the original authors and the translator have written the book from the particular point of view to which they adhere, yet in their critical evaluation of all the work on the subject, they have been eminently fair. The concept of the renal, and probably humoral, origin of most cases of so-called essential hypertension dominates the book, but an excellent historical survey is included and a good discussion of all other views is given. No brief summary of this book, which would be of any value, is possible. An important part of the book for other investigators is the appendix, which gives the details of the various methods developed and used by the authors in their own studies of experimental renal and human hypertension, especially the preparation and assay of the various constituents of the humoral mechanism. Since Dr. Dexter states that he did not attempt "To produce a line for line translation of the book," no comment on the exactness of this translation is necessary. Although the reviewer is unfamiliar with Spanish, yet his knowledge of the important contributions of the authors to the subject of hypertension makes it possible for him to state unequivocally that Dr. Dexter has certainly presented a correct version of their views. The book is well written and the illustrations, although many are reproductions of illustrations in other books and journals, are well chosen and entirely adequate. This book should be regarded as an outstanding contribution to the subject of hypertension in general and experimental renal hypertension in particular.

HARRY GOLDBLATT.

On Oct. 16, 1946, occurred the first public demonstration of the relief of the pain of surgery by ether vapors. The Centenary of this great contribution to the world is being commemorated by three publications which will be reviewed here.

VICTORY OVER PAIN. By Victor Robinson, M.D. New York, 1946, Schuman's ed 1.

This is a history of anesthesia ostensibly, but it is far more than that. Dr. Robinson has a stirring tale to tell and does full justice to it. Drama, controversy, despair, and bitterness, as well as triumph, characterize the volume. The great characters in medicine of the nineteenth century relive. American, English, Scottish, French, German, and Russian medical circles are portrayed with fascinating detail. The presentation abounds with anecdotes and with letters interpreted with insight and perspective. The whole story is humanized by a master of medical history. *Victory Over Pain* should be required reading for physicians, and also for thinking people in all circles. It recounts the hazards and disappointments of research. It emphasizes the price of the failure to recognize the significance of new observations. It describes the struggles for fame and fortune occasioned by the difficulty of establishing priority for a discovery. More than this, the book can be regarded as contributing to our understanding of the relationship of the sciences to humanity.

As stated by the publishers, "We are all aware that scientific advances have reached a point where they dominate the lives and destiny of everyone. With this awareness has come a natural desire to understand more fully the role and impact of science on our everyday life." Anesthesia must be considered among the major contributions of man to his fellow men. It is fitting and proper that its story be recounted for all to appreciate.

Readable, lucid, instructive and entertaining, this volume is unhesitatingly recommended to physicians whatever their special interest.

ROBERT D. DRIPPS, M.D.

A MEMOIR ON A NEW USE OF SULFURIC ETHER. By W. T. G. Morton. New York, 1946, Schuman's.

For one hundred years the controversy over who discovered and introduced surgical anesthesia has continued. Long, Wells, Jackson, and Morton have been the chief figures in this unfortunate dispute. This little monograph presents Morton's attempt to justify his claims. It is the first separate reprinting of his celebrated letter to the Academy of Sciences at Paris. The reprinting is amply justified as a contribution to the ether centennial. It strongly supports the contention of those who establish William T. Green Morton as the individual who first realized the *significance* of the ability of ether to relieve the pain of surgical intervention.

ROBERT D. DRIPPS, M.D.

THE CENTENNIAL OF SURGICAL ANESTHESIA, AN ANNOTATED CATALOGUE. Compiled by John F. Fulton, M.D., and Madeline E. Stanton, A.B. New York, 1946, Schuman's.

The final contribution by this particular publisher to the ether centennial is the annotated catalogue of the early writings on anesthesia prepared for an exhibit at the Yale School of Medicine. There is an introduction and pertinent comment by John F. Fulton, Professor of Physiology at Yale. This catalogue would be of interest primarily to historians or others concerned with the details of the story of anesthesia.

ROBERT D. DRIPPS, M.D.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.